

# **EXHIBIT J**

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY

IN RE: VALSARTAN, : MDL NO. 2875  
LOSARTAN, AND :  
IRBESARTAN PRODUCTS : HON. ROBERT  
LIABILITY LITIGATION : B. KUGLER

THIS DOCUMENT APPLIES :  
TO ALL CASES :

- CONFIDENTIAL INFORMATION -  
SUBJECT TO PROTECTIVE ORDER

September 16, 2021

Videotaped remote deposition of MICHAEL B. BOTTORFF, Pharm.D., taken pursuant to notice, was held via Zoom Videoconference, beginning at 9:04 a.m., EST, on the above date, before Michelle L. Gray, a Registered Professional Reporter, Certified Shorthand Reporter, Certified Realtime Reporter, and Notary Public.

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Testimony of:

MICHAEL B. BOTTORFF, Pharm.D.

By Mr. Vaughn 11, 370  
By Ms. Thompson 356

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THE VIDEOGRAPHER: We are now on the record. My name is Judy Diaz. I'm a legal videographer for Golkow Litigation Services.

Today's date is September 16, 2021, and the time is 9:04 a.m.

This remote video deposition is being held in the matter of Valsartan, Losartan, and Irbesartan Products Liability Litigation MDL for the United States District Court District of New Jersey.

The deponent is Dr. Michael Bottorff.

All parties to this deposition are appearing remotely and have agreed to the witness being sworn in remotely.

All counsel will be noted on the stenographic record.

1                   The court reporter is  
2                   Michelle Gray and will now swear  
3                   in the witness.

4                                 -   -   -

5                   ... MICHAEL B. BOTTORFF, Pharm.D.,  
6                   having been first duly sworn, was  
7                   examined and testified as follows:

8                                 -   -   -

9   EXAMINATION

10                                -   -   -

11           BY MR. VAUGHN:

12                   Q.     Doctor, can you introduce  
13                   yourself for the jury?

14                   A.     Yes.   Michael Bottorff.

15                   Q.     And am I saying it right,  
16                   Bottorff?

17                   A.     That's good.

18                   Q.     All right.   I'll try my best  
19                   not to butcher that.

20                   A.     No problem.

21                   Q.     Have you ever had your  
22                   deposition taken before?

23                   A.     I'm sorry.   The question?

24                   Q.     Have you previously had your

1 deposition taken in any matter?

2 A. Yes, I have.

3 Q. Was that a yes?

4 A. Yes.

5 Q. And what litigations were  
6 those?

7 A. There was an amiodarone  
8 litigation that I think we've disclosed.  
9 That's the only one that's been in the  
10 last maybe four or five years. Prior to  
11 that I did some depositions in Niaspan  
12 patent law. And then a couple of  
13 personal injury depositions probably back  
14 in the 1990s.

15 Q. Okay. There's only -- was  
16 the first one a drug case that you were  
17 an expert in?

18 A. In the '90s, yes.

19 Q. And were you on the  
20 plaintiffs' or the defense side?

21 A. Defense.

22 Q. And have you ever had your  
23 deposition taken via Zoom before?

24 A. No.

1 Q. If you have any problems  
2 hearing me just let me know. Okay?

3 A. I will.

4 Q. All right. And then for the  
5 court reporter's sake, let's try our best  
6 not to talk over each other and give, you  
7 know, the defense attorney time to make  
8 her objections, if she has any. Is that  
9 fair?

10 A. Yes.

11 Q. And do you understand that  
12 if there are objections, those are just  
13 between the defense attorney and myself  
14 and they shouldn't influence your answers  
15 in any way?

16 A. I understand.

17 Q. And you're an expert for the  
18 defense in this litigation, correct?

19 A. Correct.

20 Q. And as an expert, you're  
21 aware that I'm allowed to ask you  
22 hypothetical questions, right?

23 A. Yes.

24 Q. And if you don't understand

1 my questions, you'll let me know, right?

2 A. I will.

3 Q. Okay. So I want to explore  
4 just some of your opinions first and the  
5 basis for those opinions. And so, kind  
6 of reading through here, I guess my first  
7 question is, Dr. Bottorff, is it your  
8 opinion that generic valsartan  
9 contaminated with NDMA or NDEA has the  
10 same monetary value as generic valsartan  
11 without NDMA or NDEA?

12 MS. THOMPSON: Objection.  
13 Form. Compound.

14 THE WITNESS: So the  
15 question, as I understand it, is  
16 the same monetary value?

17 BY MR. VAUGHN:

18 Q. Correct.

19 A. I believe it would be.

20 Q. And what's the basis for  
21 your opinion on that?

22 A. Because I don't see how it  
23 substantially changed the effectiveness  
24 of the drug.

1 Q. And what do you mean by the  
2 effectiveness of the drug?

3 A. Its ability to do what it  
4 was intended to do, which was control  
5 heart failure, hypertension post-MI.

6 Q. And is it your opinion that  
7 the levels of NDMA in generic valsartan  
8 are unable to increase a person's risk of  
9 developing cancer?

10 MS. THOMPSON: Objection.  
11 Form.

12 THE WITNESS: I don't think  
13 I'd characterize my opinion as  
14 being unable. I don't think I  
15 used those terms anywhere.

16 BY MR. VAUGHN:

17 Q. What is your opinion as to  
18 if the levels of NDMA contained in  
19 generic valsartan can increase the  
20 levels -- increase the risk of someone  
21 developing cancer?

22 MS. THOMPSON: Objection.  
23 Form.

24 THE WITNESS: We don't have



1           the answer to that because we  
2           don't have adequate data in humans  
3           to make that determination.

4   BY MR. VAUGHN:

5           Q.     If the levels of NDMA in  
6           generic valsartan did increase the risk  
7           of someone developing cancer, would you  
8           agree that it would reduce the monetary  
9           value of that medication?

10           MS. THOMPSON:  Objection.  
11           Form.  He wasn't designated on  
12           issues of monetary value.  So  
13           I'm --

14           MR. VAUGHN:  He just said --  
15           he just told me that he had an  
16           opinion on it, so I'm exploring  
17           that opinion.

18           THE WITNESS:  Yeah, I don't  
19           really -- it wasn't any of the  
20           focus that I used in my  
21           evaluation.

22                    So I haven't really  
23           expressed any kind of opinion on  
24           monetary, other than I don't think

1           it would have altered its  
2           effectiveness and not necessarily  
3           another step of whatever that  
4           monetary value would be.

5       BY MR. VAUGHN:

6           Q.       Okay. So you do not plan to  
7           tell the jury that the monetary value of  
8           valsartan contaminated with NDMA is  
9           unchanged?

10          A.       I have no plans on talking  
11          about monetary value.

12          Q.       Okay. Do you think it's  
13          acceptable for a patient to take generic  
14          valsartan at the highest levels of  
15          contamination of NDMA that we've seen?

16                   MS. THOMPSON: Objection.  
17          Form.

18                   THE WITNESS: Well, again,  
19          I'm not sure exactly what you're  
20          asking.

21                   What I have formed an  
22          opinion on and provided in my  
23          report is that I don't believe  
24          there's any -- any risk associated

1 with the amount of NDMA that's in  
2 any of the valsartan products that  
3 I evaluated.

4 BY MR. VAUGHN:

5 Q. And what amount of NDMA  
6 would be necessary in valsartan to  
7 increase the risk of someone developing  
8 cancer?

9 A. In humans, we don't have  
10 that answer. We're having to completely  
11 rely on animal data to make any kind of  
12 extrapolation along those lines at all.

13 And I think we've seen in  
14 the literature multiple people express  
15 concerns about extrapolating animal data  
16 to human data.

17 I did in my report try to  
18 do, based on the available data with all  
19 those known limitations, suggest that the  
20 amount of what I'm going to call  
21 impurities of NDMA in any of the  
22 valsartan products seems well below what  
23 in the animal studies might be expected  
24 to cause any cancer.

1 Q. And so do you not have an  
2 opinion as to how much NDMA it would take  
3 to increase the risk of someone  
4 developing cancer?

5 MS. THOMPSON: Objection.  
6 Form. And again, this is not what  
7 he was designated on.

8 THE WITNESS: Yeah, I don't  
9 think that's what any focus on my  
10 report was on.

11 MR. VAUGHN: Tyler, can you  
12 pull up his expert report for me.

13 TRIAL TECH: Sure. Give me  
14 one second.

15 (Document marked for  
16 identification as Exhibit  
17 Bottorff-1.)

18 MS. THOMPSON: We're giving  
19 him a hard copy of his report as  
20 well.

21 MR. VAUGHN: Sounds good.  
22 Tyler, can we go to Page 63  
23 of this report.

24 TRIAL TECH: Sure. And this

1 will be Exhibit 1.

2 MR. VAUGHN: Yeah. Thank  
3 you for that.

4 TRIAL TECH: No problem.  
5 You said Page 63?

6 MR. VAUGHN: Yeah.

7 BY MR. VAUGHN:

8 Q. And Dr. Bottorff, let me  
9 know when you're there.

10 A. I am. I'm there now.

11 Q. Can you read looks like  
12 Opinion VII..?

13 Can you read it out loud?  
14 I'm sorry.

15 A. Yes, I will.

16 "The scientific literature  
17 and evidence, which I have reviewed  
18 extensively, do not support that the  
19 valsartan products during the time period  
20 at issue carried an independent risk of  
21 cancer, nor that there is any increased  
22 risk of cancer associated with the  
23 valsartan containing the NDMA/NDEA  
24 impurity as compared to valsartan with a

1 zero level of NDMA or NDEA."

2 Q. Okay. Would you agree with  
3 me that you're giving an opinion that the  
4 levels of NDMA do not increase the risk  
5 of a patient's cancer?

6 A. Yes. But I thought your  
7 question was, how much would it take to  
8 cause cancer. And I didn't have a good  
9 answer to that.

10 MS. THOMPSON: I was trying  
11 to get an objection in there.

12 THE WITNESS: Oh, sorry.

13 MR. VAUGHN: So reminder to  
14 give me a pause.

15 I was objecting to the form  
16 of the last question.

17 THE WITNESS: Sorry.

18 BY MR. VAUGHN:

19 Q. Doctor, is it your opinion  
20 that no level of NDMA would cause cancer  
21 in a human?

22 MS. THOMPSON: Objection.  
23 Form.

24 THE WITNESS: I don't know

1 the answer to that. We don't have  
2 any data on what it would take to  
3 cause cancer in humans with drugs  
4 that haven't been -- or compounds  
5 that haven't been studied in  
6 humans.

7 BY MR. VAUGHN:

8 Q. If you do not know the level  
9 that would -- of NDMA that it would take  
10 to cause cancer, how can you give an  
11 opinion that the levels of NDMA in  
12 valsartan cannot increase the risk of  
13 someone developing cancer?

14 MS. THOMPSON: Objection.  
15 Form.

16 THE WITNESS: Again, as I  
17 said before, we're having to  
18 extrapolate the animal data with  
19 all those known limitations.

20 And so, this statement was  
21 based on how much NDMA did not  
22 seem to cause cancer in animals.

23 And that was in many cases  
24 way above the amount that's in any

1 of these valsartan products.

2 So again, accepting those  
3 limitations, that's where this  
4 conclusion comes from.

5 BY MR. VAUGHN:

6 Q. So you're not able to tell  
7 our jury at what point -- at what level  
8 NDMA in valsartan would increase the risk  
9 of someone developing cancer?

10 A. Yeah. I don't think there's  
11 anybody who can do that.

12 Q. What is the highest level of  
13 NDMA that you're aware of in generic  
14 valsartan?

15 A. I can look at my report,  
16 which I think --

17 Q. Take your time.

18 A. No problem. Just scanning  
19 through the NDMA amounts on Page 6, 7,  
20 and 8 of my report, the highest amount, I  
21 think, was just over 20 micrograms.

22 Q. So is it safe -- I'm sorry.

23 A. I was just going to add, in  
24 a valsartan 320-milligram tablet.



1 Q. I appreciate that.

2 And so the opinions in your  
3 expert report only apply to a daily NDMA  
4 exposure level of 20 micrograms or lower?

5 MS. THOMPSON: Objection to  
6 form.

7 THE WITNESS: Sorry. I'm  
8 not -- that's not exactly what I  
9 say in my report.

10 BY MR. VAUGHN:

11 Q. What is it -- how did I  
12 mischaracterize it?

13 A. If we go to Page 32 and 33,  
14 which is where I make that extrapolation  
15 from -- this is one study, for example,  
16 by Ito that there was an animal dose that  
17 did not produce cancers, and  
18 extrapolating that in kilogram to the  
19 human exposure, if you use the same  
20 milligram per kilogram calculation,  
21 again, with all those limitations, then  
22 the amount that was not cancer causing in  
23 this study were anywhere from  
24 approximately 300 to over 20,000 times

1 the amount that's in any of the valsartan  
2 products.

3 Q. We'll get more into that in  
4 a little bit. But in forming your expert  
5 opinions, the highest level of NDMA that  
6 you were aware of in valsartan was  
7 20 micrograms, correct?

8 A. Correct.

9 MR. VAUGHN: Can we go to --  
10 back to Page 6 real quick, Tyler.

11 BY MR. VAUGHN:

12 Q. All right. On that second  
13 paragraph, Doctor, you note that there's  
14 levels as high as 120 parts per million.  
15 Where did that information come from?

16 A. I'm assuming that it's a  
17 part per million conversion from these  
18 data, from the FDA's laboratory analysis.

19 Q. Where did you find that data  
20 though? Where did you find the 120 parts  
21 per million? Are you the one that did  
22 that calculation?

23 A. No. I wouldn't have done  
24 the calculation.

1 Q. So where did you find that  
2 information? I don't see a citation. So  
3 I'm just wondering where this came from?

4 A. I don't recall exactly.

5 Q. What did you say ppm stands  
6 for?

7 A. Parts per million.

8 Q. Okay. And you would expect  
9 that that part per million, if you  
10 actually do the math to figure out how  
11 many micrograms that could be in a pill  
12 of valsartan, would be no more than  
13 20 micrograms, right?

14 A. If this range is  
15 representative of what the FDA's analysis  
16 is, then that would be correct.

17 Q. But you're not sure where  
18 this range even comes from?

19 MS. THOMPSON: Objection to  
20 form.

21 THE WITNESS: No.

22 Sorry.

23 My best guess at this point  
24 in time is that those are the

1 ranges that were also in the FDA's  
2 testing, but I don't recall it  
3 exactly at this point.

4 BY MR. VAUGHN:

5 Q. Okay. Doctor, are you aware  
6 how to convert parts per million into  
7 micrograms or nanograms in a pill?

8 A. Yes, it's based on the  
9 milligram strength of the tablet that  
10 that's calculated.

11 Q. And how many nanograms --  
12 are you aware of how many nanograms are  
13 in a milligram?

14 A. Yes.

15 Q. How many?

16 A. A milligram has a thousand  
17 micrograms, which also has a thousand  
18 nanograms per microgram. So that would  
19 be about a million.

20 Q. It would be one million?

21 A. Yes.

22 Q. And so for every milligram  
23 of valsartan, there would be 120  
24 nanograms of NDMA; is that correct?

1           A.     I think that's the correct  
2     calculation.

3                     MR. VAUGHN:   Tyler, can you  
4             pull a calculator up for us.

5     BY MR. VAUGHN:

6           Q.     All right.   And how --  
7     before we do this, 20 micrograms, how  
8     many nanograms would that be?

9           A.     20,000.

10          Q.     20,000.   Okay.   So let's  
11     take the 120 -- let me see if I can --  
12     there we go.   120 was the parts per  
13     million.   Oh, didn't want that to happen.  
14                     120.

15                     And what's the largest dose  
16     of valsartan?

17          A.     320 milligrams.

18          Q.     One second.

19                     120 times -- did you say 320  
20     was the largest?

21          A.     Correct.

22                     MR. VAUGHN:   Hey, Tyler, can  
23             you try and control this?   It's  
24             not working for me.

1 TRIAL TECH: Yeah, I think  
2 you just need to clear -- do it  
3 120.

4 MR. VAUGHN: Times 320.

5 TRIAL TECH: Where is --  
6 okay, now it's clear. 120 times  
7 320.

8 There you go.

9 BY MR. VAUGHN:

10 Q. That's 38,400 nanograms,  
11 correct, Doctor?

12 A. Yes.

13 Q. And how many micrograms  
14 would that be?

15 A. 38.4.

16 Q. And would you agree with me  
17 that's approximately twice as high as any  
18 of the levels the FDA identified?

19 MS. THOMPSON: Objection.  
20 Form.

21 THE WITNESS: Yeah, so I'm  
22 guessing that was ZHP's own  
23 analysis and not the FDA's  
24 analysis where that separate range

1 of 120 came from.

2 BY MR. VAUGHN:

3 Q. Did you review ZHP's  
4 analysis?

5 A. I think it's -- I think it's  
6 in my reliance documents.

7 Q. Okay. Do you remember any  
8 levels higher than 120 parts per million  
9 in ZHP's analysis?

10 A. I do not.

11 If you -- if I can just  
12 expand a little bit. If I recall, ZHP's  
13 analysis was based on the parts per  
14 million of their API, which would be the  
15 small amount of milligrams of the active  
16 ingredient.

17 So I don't know if that  
18 changes the calculation or not.

19 Q. Can you explain to me what  
20 API is?

21 A. The active ingredient.

22 Q. And what's the active  
23 ingredient in valsartan?

24 A. Valsartan.

1 Q. Okay. And the final pill,  
2 what is it made up of besides valsartan  
3 and sometimes NDMA and NDEA?

4 MS. THOMPSON: Objection to  
5 form.

6 THE WITNESS: Off the top of  
7 my head, I don't know that  
8 exactly. But I can tell you,  
9 having been trained in pharmacy,  
10 that it will have all kinds of  
11 binders and other excipients and  
12 lubricants so it flows through  
13 machines when they make the  
14 tablets and that kind of thing.

15 BY MR. VAUGHN:

16 Q. So a 320-milligram valsartan  
17 pill will have 320 milligrams of  
18 valsartan in it, correct?

19 A. Correct.

20 Q. But will the total pill be  
21 more than 320 milligrams because it has  
22 other constituents in it?

23 A. It would have to be.

24 Q. Okay. And so if ZHP's parts



1 per million is on the API of valsartan,  
2 how does that make a difference now when  
3 we're going to the final pill if there's  
4 still 320 milligrams in there?

5 A. It's part of the same part  
6 per million calculation. But I don't  
7 know how that changes when the API gets  
8 incorporated in -- into the tablet.

9 Q. Okay. But the final tablet  
10 would be more than 320 milligrams, right?

11 A. Right.

12 Q. Do you have any idea, like,  
13 as a pharmacist, on average, what  
14 percentage of a pill is filler?

15 A. I haven't looked at that  
16 kind of calculation in, gosh, years,  
17 because it's never really been called  
18 into question or needed to be known.

19 Q. And so, in forming your  
20 opinions in this litigation, you didn't  
21 consider the amount of filler in  
22 valsartan, correct?

23 MS. THOMPSON: Objection to  
24 form.

1 THE WITNESS: Correct.

2 Sorry.

3 I did not.

4 BY MR. VAUGHN:

5 Q. If someone were to test a  
6 pill, the parts per million would be  
7 lower than if they tested the API,  
8 correct?

9 A. You know, at this point I'm  
10 not sure, because if it's based on the  
11 320 milligrams of active ingredient,  
12 seems like the calculation would still be  
13 the same.

14 Q. Well, let's say a pill is  
15 640 milligrams but only half of that is  
16 valsartan, would that not half the parts  
17 per million of the NDMA in the pill?

18 MS. THOMPSON: Objection to  
19 form.

20 THE WITNESS: If you based  
21 it on the weight of the actual  
22 pill instead of based on the  
23 active ingredient.

24 BY MR. VAUGHN:

1 Q. And if you didn't know the  
2 percentages of what the filler were, what  
3 would you -- how could you base it on  
4 anything but the entire pill's weight?

5 A. Well, I think the issue at  
6 hand was the part per million of the  
7 valsartan and not the ppm based on any of  
8 the excipients or anything else.

9 Q. So would you agree with me  
10 that it would be more appropriate to use  
11 the ppm of the API than the final  
12 product?

13 A. I would agree with that.

14 MR. VAUGHN: Tyler, can we  
15 go back to --

16 Can you guys all hear me?  
17 It says my connection is unstable  
18 right now.

19 Okay. Tyler can we go back  
20 to Page 6 of this expert report.

21 Zoom out a little bit.

22 BY MR. VAUGHN:

23 Q. You note here, the fourth  
24 column on the right, midpoint --

1 MR. VAUGHN: And if we go to  
2 the next page, Tyler.

3 BY MR. VAUGHN:

4 Q. It looks like you calculated  
5 the midpoint of the contamination; is  
6 that correct?

7 MS. THOMPSON: Objection to  
8 form.

9 THE WITNESS: Correct.

10 BY MR. VAUGHN:

11 Q. Why did you calculate the  
12 midpoint?

13 A. It was an attempt to try to  
14 represent that it would be unlikely over  
15 the three to four or whatever years of  
16 exposure at the time that these  
17 impurities were known to be in valsartan  
18 tablets that someone would take the exact  
19 same lot for the entire period of time  
20 that they were on that particular dose of  
21 valsartan.

22 And so they would have, even  
23 within the same manufacturer, probable  
24 exposure to a different lot that had a

1 different amount and/or be switched over,  
2 depending on what the pharmacy was  
3 carrying at the time, to another product  
4 that had a different amount.

5 So it was really just to try  
6 to give an idea. You have the lowest  
7 amount that could be found, which in many  
8 cases was below the lower limits of  
9 detection, and the highest amount that  
10 was found in one of the products.

11 But the reality is that an  
12 exposure value might actually be  
13 something that's more of a midpoint.

14 Q. Do you know how the FDA came  
15 to these results?

16 A. In terms of the analytical  
17 process?

18 Q. Yeah. I mean, were they  
19 testing the whole pill or were they  
20 testing the API?

21 A. I think they could only have  
22 been testing the full pill.

23 Q. And have you seen any  
24 evidence that the FDA considered how much

1 filler is in the pill?

2 A. I've not seen that anywhere.

3 Q. A midpoint isn't the same as  
4 the average, correct?

5 A. Correct. Which is why I did  
6 not put the average in there, is you  
7 don't have the raw data to be able to  
8 accurately calculate an average.

9 Q. Did the defense attorneys  
10 not provide you the raw data?

11 MS. THOMPSON: Objection.  
12 Form.

13 THE WITNESS: No. I went  
14 off this, which was the FDA's  
15 report. And if you don't have  
16 each individual result for each  
17 individual tablet, and you just  
18 have an upper and lower limit of  
19 the range, you can't guesstimate  
20 how many that was involving to be  
21 able to calculate statistically an  
22 average.

23 BY MR. VAUGHN:

24 Q. Did you not ask defense

1 counsel to provide you all the levels of  
2 the internal testing?

3 MS. THOMPSON: Objection.  
4 Form.

5 THE WITNESS: I did not.

6 BY MR. VAUGHN:

7 Q. Why?

8 A. I had no reason to.

9 Q. I'm sorry. You didn't  
10 consider any of the internal testing in  
11 forming your opinions?

12 MS. THOMPSON: Objection.  
13 Form.

14 THE WITNESS: No. That is  
15 in my report. It is what I  
16 considered for the amounts  
17 contained in the valsartan  
18 products.

19 BY MR. VAUGHN:

20 Q. What if the internal testing  
21 shows much higher levels than this?

22 MS. THOMPSON: Objection.  
23 Form.

24 THE WITNESS: I don't have

1           that data, so I don't know.

2       BY MR. VAUGHN:

3           Q.     So your opinions won't apply  
4     to it if the -- to the levels if they  
5     were higher than what's in the FDA's?

6           A.     It would depend how much  
7     higher. And I'd have to see them.

8           Q.     How much higher?

9           A.     I don't know. I'd have to  
10    see it.

11          Q.     You said it depends on how  
12    much higher. At what point does it  
13    matter?

14                 MS. THOMPSON: Objection.  
15                 Form.

16                 THE WITNESS: Again, I'd  
17    have to see them and then be able  
18    to make that determination.

19       BY MR. VAUGHN:

20          Q.     Is there any level that  
21    you're going to say is unacceptable?

22                 MS. THOMPSON: Objection  
23                 form.

24                 THE WITNESS: I believe



1           you've asked that, and my answer  
2           was I don't think there is a level  
3           that I can say is going to be  
4           related to cancer in humans,  
5           because we don't know that. We  
6           don't have that data.

7       BY MR. VAUGHN:

8           Q.       So it's irrelevant to you  
9           how much NDMA is in valsartan?

10                   MS. THOMPSON: Objection.  
11           Form. Mischaracterizes testimony.

12                   THE WITNESS: Yeah, I don't  
13           think I ever used the word  
14           "irrelevant."

15       BY MR. VAUGHN:

16           Q.       Is there any point when you  
17           would be concerned on the level of NDMA  
18           in valsartan?

19                   MS. THOMPSON: Objection.  
20           Form.

21                   THE WITNESS: Yeah, I don't  
22           really know what you're trying to  
23           get me to say or what you're  
24           really asking.

1 I'm concerned with the  
2 amounts that I know, based on the  
3 FDA's analysis, were in valsartan  
4 tablets, and then comparing that  
5 to the animal data, which is all  
6 we have, to see if I believe that  
7 this exceeded the metabolic  
8 capacity -- and this is from a  
9 pure pharmacokinetic drug  
10 metabolism standpoint -- that has  
11 been associated in animal studies  
12 with not causing cancer.

13 So I wasn't looking to try  
14 to establish an amount that would  
15 cause cancer. So I don't have an  
16 opinion on that.

17 BY MR. VAUGHN:

18 Q. You weren't trying to figure  
19 out how much NDMA it would take to cause  
20 cancer in humans?

21 A. No. I was not.

22 Q. Okay. And in forming your  
23 opinions, you assumed that the FDA's  
24 analysis is actually the highest levels

1 of NDMA engineered in valsartan, correct?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: I did not

5 assume that.

6 BY MR. VAUGHN:

7 Q. So you think that there  
8 might be actually higher levels than the  
9 FDA is aware of?

10 MS. THOMPSON: Objection to  
11 form.

12 THE WITNESS: I don't know.  
13 This is what I had to go off of,  
14 based on the FDA's published data.

15 BY MR. VAUGHN:

16 Q. So why is that not assuming  
17 the highest levels? You didn't even ask  
18 for the internal data.

19 A. I wasn't assuming anything.  
20 I was evaluating what I had access to.

21 Q. Doctor, were you initially  
22 retained for this litigation by Teva?

23 A. No one from Teva has ever  
24 contacted me.

1 Q. Were you initially retained  
2 for this litigation for every defendant  
3 or a specific defendant?

4 A. I think when I was  
5 originally retained, the word Teva may  
6 have been mentioned in some of those  
7 early communications. But since then  
8 there's never been any contact directly  
9 with Teva at all.

10 Q. Okay. So you do think you  
11 might have initially been retained by  
12 Teva?

13 A. No. I didn't say that.  
14 I've only been retained by  
15 GT. And they may have mentioned that  
16 Teva was one of the defendants in some of  
17 the earlier communication. But since  
18 then, I understand that there are other  
19 defendants in this as well.

20 Q. When were you initially  
21 retained for this litigation?

22 A. It was either right at the  
23 end of 2020 or the very early part of  
24 2021.

1 Q. And approximately when did  
2 you become aware of all the other  
3 defendants?

4 A. I -- I don't have a date for  
5 that. Probably sometime in the spring.

6 MR. VAUGHN: Okay. Tyler,  
7 can we go to -- I think it's  
8 Exhibit B on my files. It's -- or  
9 exhibit -- one second. Yeah,  
10 Exhibit B of his expert report.

11 And then can we go to  
12 Page 10.

13 (Document marked for  
14 identification as Exhibit  
15 Bottorff-2.)

16 BY MR. VAUGHN:

17 Q. All right. We'll see down  
18 here some Teva Bates numbers.

19 MR. VAUGHN: And then,  
20 Tyler, can we go to the next page.

21 BY MR. VAUGHN:

22 Q. And then a bunch more Teva  
23 Bates numbers.

24 MR. VAUGHN: Next page,

1 Tyler.

2 BY MR. VAUGHN:

3 Q. A bunch more Teva.

4 MR. VAUGHN: Next page.

5 BY MR. VAUGHN:

6 Q. A bunch more Teva.

7 MR. VAUGHN: Next page.

8 BY MR. VAUGHN:

9 Q. All Teva again.

10 MR. VAUGHN: Next page.

11 BY MR. VAUGHN:

12 Q. And then there's two other  
13 Bates numbers here. There's HLL. Do you  
14 know what the HLL Bates numbers denote,  
15 Doctor?

16 A. Is that on this screen that  
17 I'm looking at?

18 Q. Yeah. The top right-hand  
19 corner. It's the only ones that didn't  
20 have a Teva Bates number. I didn't know  
21 if you knew what company's documents  
22 those two are.

23 MS. THOMPSON: Objection.

24 Form.

1 THE WITNESS: I -- I assume  
2 they're associated with what's on  
3 the left hand column.

4 BY MR. VAUGHN:

5 Q. Okay. So did you only  
6 review internal documents of Teva in this  
7 litigation?

8 MR. VAUGHN: Is that my  
9 internet or his that's messing up?  
10 He's frozen on my screen.

11 THE VIDEOGRAPHER: He looks  
12 frozen on my screen.

13 THE WITNESS: Oh, well.

14 THE VIDEOGRAPHER: Oh, yeah,  
15 he's back.

16 BY MR. VAUGHN:

17 Q. Okay. I'm sorry, Doctor. I  
18 missed whatever your answer was.

19 A. I didn't yet because you  
20 said I was frozen so --

21 Q. Okay.

22 A. -- I didn't think you could  
23 hear me either.

24 Q. I appreciate it.

1           A.       In looking at these  
2 documents, my recollection back then, I  
3 think the first round of materials that  
4 were provided to me were probably Teva  
5 materials.

6           Q.       Were any of those internal  
7 testing by Teva?

8           A.       They may have been. I don't  
9 recall specifically.

10          Q.       You didn't review any other  
11 documents of any other defendant besides  
12 Teva, did you?

13          A.       No, I don't believe so.

14          Q.       Why did you only review Teva  
15 documents?

16          A.       The question that I was  
17 specifically addressing didn't seem to be  
18 as important to be looking at internal  
19 documents for every single defendant as  
20 opposed to evaluating the literature for  
21 NDMA, NDEA metabolism and distribution.

22          Q.       Well, then why did you  
23 review Teva documents?

24                   MS. THOMPSON: Objection.



1 Form.

2 THE WITNESS: They were sent  
3 to me early on. And when I  
4 receive documents, I reviewed  
5 them.

6 BY MR. VAUGHN:

7 Q. Are these the documents that  
8 you requested, or they just picked out  
9 documents and sent to you?

10 MS. THOMPSON: Objection to  
11 form.

12 THE WITNESS: I didn't  
13 request them, so they were somehow  
14 selected and sent to me.

15 MR. VAUGHN: We can take  
16 down the exhibit. I'm done with  
17 that for now.

18 BY MR. VAUGHN:

19 Q. Doctor, what degrees do you  
20 hold?

21 A. I hold a bachelor's degree  
22 from Georgia Tech, and PharmD degree from  
23 the University of Kentucky.

24 Q. You're a pharmacist?

1 A. Yes.

2 Q. When you're filling a  
3 medication for someone, what do you call  
4 that person that you're filling the  
5 medication for? For instance, are they  
6 your client, a customer, a patient?

7 A. Well, they would be a  
8 patient in my reference. But that's not  
9 been what my career has been, is filling  
10 prescriptions, that type of pharmacist.

11 Q. Have you ever filled a  
12 prescription?

13 A. Yes.

14 Q. When was the last time that  
15 you did that?

16 A. Probably the summer of 1982.

17 Q. If you're not filling  
18 prescriptions, what is it that you do for  
19 work?

20 A. My career has always been in  
21 academic pharmacy. So certainly teaching  
22 has been part of that. But as part of  
23 that, I had a clinical practice where I  
24 rounded with an interdisciplinary

1 cardiology team on inpatients at academic  
2 medical centers for 35 years.

3 Q. What do you currently do for  
4 work?

5 A. What I thought was going to  
6 be a semi-state of retirement has turned  
7 out to be almost full-time, because I'm  
8 continuing to teach for my most recent  
9 academic appointment at Manchester  
10 University in Fort Wayne, Indiana. And  
11 certainly Covid has allowed a lot of  
12 online teaching to be done, so I didn't  
13 have to be in Indiana all the time to do  
14 that.

15 And then I -- the position  
16 that I was in prior to that was in  
17 Knoxville at South College. And I'm now  
18 chair of their independent research  
19 committee.

20 And then most recently I've  
21 been added to the adjunct faculty the  
22 University of Cincinnati where I used to  
23 teach for 20 years to be involved in  
24 their online Masters in pharmacogenomics

1 program.

2 Q. At Manchester University,  
3 are you a professor or an adjunct  
4 professor?

5 A. As of last August, I am  
6 adjunct. And I was professor for five  
7 years prior to that.

8 Q. What is an adjunct  
9 professor? What's the difference of that  
10 and a professor?

11 A. A pay cut basically.  
12 You know, going to some more  
13 of what would be called a part-time  
14 status. Still paid, but part-time  
15 status.

16 Q. Okay. How many hours a week  
17 are you -- do you devote to the adjunct  
18 professor?

19 A. For Manchester, probably 15.  
20 For University of Cincinnati probably  
21 five to ten depending on when things are  
22 being done that are -- or what I'm being  
23 expected to do.

24 Q. How many students do you

1 currently teach?

2 A. There are roughly 65 in each  
3 class of the four years of pharmacy  
4 students at Manchester. And the online  
5 genomics program has just started at  
6 Cincinnati, so it is a smaller program.  
7 I think it has like eight to ten.

8 Q. Okay. What is  
9 pharmacogenomics? Can you explain that?

10 A. Yeah. It's the study of the  
11 interaction between genetic alterations  
12 in drug metabolism or response and the  
13 drugs that are being given to patients.

14 So it is a component of sort  
15 of a common buzzword these days called  
16 personalized medicine.

17 Q. And so is the focus on it  
18 specifically pharmacological drugs, not  
19 carcinogens?

20 A. All drugs.

21 Q. Are there drugs that are  
22 carcinogens?

23 A. Yes.

24 Q. Such as?

1           A.       Immunosuppressant drugs for  
2 transplant patients have the ability to  
3 induce cancers by blocking cancer sort of  
4 surveillance systems.

5           Q.       How do they block cancer  
6 surveillance systems?

7           A.       They're immunosuppressants.  
8 And as part of the immune system is a  
9 component of it that suppresses cancer  
10 cells.

11          Q.       So would you agree with me  
12 that an immunosuppressant increases the  
13 risk of one developing cancer?

14          A.       Yep. That's been reported.

15               MS. THOMPSON: Sorry, we  
16 have a loud air conditioner.  
17 Hopefully it will turn off soon.

18               MR. VAUGHN: I can't hear it  
19 actually.

20               MS. THOMPSON: It's loud in  
21 here.

22               MR. VAUGHN: Can we go back  
23 to the expert report, Tyler.

24               Page 3.

1 BY MR. VAUGHN:

2 Q. All right. You note during  
3 your career that you have served on  
4 advisory boards and national speaking  
5 bureaus for several pharmaceutical  
6 companies that make sartans, including  
7 Merck -- should that be losartan?

8 A. Yeah.

9 Q. And Bristol-Myers Squibb,  
10 irbesartan, and Novartis, valsartan.  
11 Were those paid positions?

12 A. Yes. Being on speakers  
13 bureaus, you're asked to give  
14 presentations and be paid for those when  
15 you go.

16 Q. Approximately in what years  
17 were you paid by these pharmaceutical  
18 companies?

19 A. Merck was the first sartan  
20 company on the market. So that would  
21 have been maybe in the mid to late '90s,  
22 irbesartan sort of in the late '90s, and  
23 valsartan, late '90s early 2000. But I  
24 haven't been on the speaker bureaus for

1 over 20 years.

2 Q. Have you done work for  
3 pharmaceutical companies within the last  
4 20 years?

5 A. What do you mean by work?

6 Q. Have you been paid by  
7 pharmaceutical companies in the last  
8 20 years outside of litigation?

9 A. A little bit. You know, if  
10 you keep up with what's happened in  
11 pharma and speaker bureaus, there's  
12 really been a pretty strict federal limit  
13 on what they used to do.

14 So I am on a couple speaker  
15 bureaus now, But for neither one of those  
16 companies have I given a talk in the last  
17 18 months because they shut those down  
18 for Covid.

19 Q. Are there any other  
20 pharmaceutical companies that make  
21 sartans that you have been paid by  
22 previously, besides the ones listed here?

23 A. No.

24 Q. How many types of sartans



1 are there?

2 A. Structural differences or in  
3 that whole category of sartans, how many  
4 of them?

5 Q. In the category of sartans.

6 A. I think there's eight or  
7 nine.

8 Q. Can you name off the ones  
9 that you recall?

10 A. Oh, there's these three.  
11 There's eprosartan. I'd have to look at  
12 a list. These are by far the more common  
13 used though.

14 Q. The eight or nine types of  
15 sartans, how many have been found to have  
16 lots that are contaminated with NDMA or  
17 NDEA?

18 MS. THOMPSON: Objection.  
19 Form.

20 THE WITNESS: To my  
21 knowledge, these three. So I've  
22 not really looked into the other  
23 ones.

24 BY MR. VAUGHN:

1 Q. And so would you agree that  
2 there are numerous sartans that are not  
3 contaminated with NDMA or NDEA?

4 A. I don't know about numerous,  
5 but I think there's some.

6 Q. Do you think there's more  
7 than there are that are contaminated?

8 MS. THOMPSON: Objection to  
9 form.

10 THE WITNESS: I don't have a  
11 breakdown because I haven't looked  
12 at the other ones that much.

13 BY MR. VAUGHN:

14 Q. Okay. So there's eight or  
15 nine types of sartans, and at least three  
16 of them that you're aware of are  
17 contaminated with a carcinogen, correct?

18 MS. THOMPSON: Objection to  
19 form.

20 THE WITNESS: Correct.

21 BY MR. VAUGHN:

22 Q. And you didn't consider the  
23 other sartans in forming your opinions in  
24 this litigation, correct?

1 A. Correct. I did not.

2 Q. And so the whole  
3 risk/benefit analysis thing that you're  
4 talking about in your report, you didn't  
5 consider the fact that there's sartans on  
6 the market that aren't contaminated with  
7 a carcinogen?

8 MS. THOMPSON: Objection to  
9 form.

10 THE WITNESS: No. I would  
11 say that's part of my  
12 consideration, is that there were  
13 potential alternatives for these  
14 three.

15 BY MR. VAUGHN:

16 Q. How many pharmaceutical  
17 companies make sartans?

18 A. I guess now that many of  
19 them are generic, there could be as many  
20 as two dozen. I don't know for sure.

21 Q. How many pharmaceutical  
22 companies make valsartan?

23 A. I don't have an exact  
24 number. I would say maybe as many as

1     ten.

2                   Q.     Can you list off the name of  
3     all the defendants in this litigation?

4                   MS. THOMPSON:   Objection.  
5                   Form.

6     BY MR. VAUGHN:

7                   Q.     Sorry.   Let me rephrase  
8     that.

9                   Can you list off all of the  
10    defendants who manufacture valsartan?

11                  A.     Well, I don't know if it's  
12    the same as what I used, which is the  
13    FDA's list of valsartan products  
14    containing the NDMA or NDEA.   But I could  
15    read those off if that's what you would  
16    like.

17                  Q.     No.   That's okay.   But your  
18    opinion is that it doesn't matter the  
19    manufacturer, none of the levels of NDMA  
20    in valsartan are going to increase  
21    someone's risk of cancer?

22                  MS. THOMPSON:   Objection.  
23                  Form.

24                  THE WITNESS:   Could you ask

1           that again? I want to be sure I  
2           answer it right.

3       BY MR. VAUGHN:

4           Q.     Is it your opinion that it  
5           doesn't matter who the manufacturer is of  
6           the generic valsartan that contains  
7           levels of NDMA; it's not going to  
8           increase someone's risk of cancer?

9                       MS. THOMPSON: Objection.  
10                      Form.

11                     THE WITNESS: The  
12           manufacturer played no role in any  
13           of my analyses. It was only the  
14           amount of NDMA or NDEA that  
15           factored into my analyses.

16       BY MR. VAUGHN:

17           Q.     But you -- so the amount of  
18           NDMA did factor into your analysis, but  
19           you're not sure if you're aware of the  
20           highest levels, correct?

21           A.     I'm sure that no one knows  
22           what the highest levels would be.

23           Q.     Would you want to know if  
24           there are levels higher than you're

1     aware -- than you are aware of in your  
2     report?

3                     MS. THOMPSON:   Objection to  
4                     form.

5                     THE WITNESS:    I suppose.    If  
6                     I had that, I could redo my  
7                     calculations and my opinions.   But  
8                     this is what I worked off of.

9     BY MR. VAUGHN:

10             Q.     If defense counsel was aware  
11             of levels higher than what you worked off  
12             of, do you think that they would have  
13             given you that information?

14                     MS. THOMPSON:   Objection.  
15                     Form.   Calls for speculation.

16                     THE WITNESS:    I have no  
17                     idea.

18     BY MR. VAUGHN:

19             Q.     Would you have expected them  
20             to give you that information?

21                     MS. THOMPSON:   Same  
22                     objection.

23                     THE WITNESS:    I guess so.

24     BY MR. VAUGHN:

1 Q. Is there a brand name of  
2 valsartan?

3 A. Diovan.

4 Q. Can you say that again? The  
5 audio broke -- cut out.

6 A. I'm sorry. The originator  
7 was --

8 Q. I'm not -- you're frozen and  
9 no audio.

10 A. Hmm.

11 Q. Oh, you're back.

12 A. Okay. The originator was  
13 Diovan with Novartis.

14 Q. Is that still on the market?

15 A. I think so.

16 Q. And are you aware if the  
17 brand name Diovan has NDMA or NDEA in it?

18 MS. THOMPSON: Objection.

19 Form.

20 THE WITNESS: I'm not aware  
21 specifically.

22 BY MR. VAUGHN:

23 Q. And so you're not aware if  
24 it's ever had it in it?

1           A.       I am not. And I know a lot  
2 of times what the originators do when the  
3 drug goes generic, is they either stop it  
4 totally or they actually get generic drug  
5 from somebody else and make their own  
6 generic. And I don't know specifically  
7 if they've done that or not.

8           Q.       You haven't looked into that  
9 in this litigation, did you?

10          A.       I did not.

11          Q.       So you have no idea if the  
12 brand name has always been completely  
13 clean of carcinogens?

14                   MS. THOMPSON: Objection.  
15                   Form.

16                   THE WITNESS: I -- I don't  
17 know that anybody knows that.

18 BY MR. VAUGHN:

19          Q.       Do you know if the  
20 manufacturing process is different?

21          A.       I didn't look into that. So  
22 I don't.

23          Q.       So as a nurse I have an  
24 ethical obligation -- had an ethical



1 obligation to patients. And, you know, a  
2 doctor has an patient relationship, and  
3 that carries certain ethical obligations.

4 Are there similar type  
5 ethical obligations a pharmacist has to  
6 the person whose medication they are  
7 filling?

8 MS. KAPKE: This is Kara  
9 Kapke. Object to form.

10 MR. VAUGHN: Are you all --  
11 I'm sorry.

12 Are all the defense  
13 attorneys going to be objecting or  
14 just one of them?

15 MS. THOMPSON: She, I  
16 believe, represents a retailer  
17 who's not part of the manufacturer  
18 group. So --

19 MR. VAUGHN: Okay. I  
20 appreciate the clarification.

21 BY MR. VAUGHN:

22 Q. So, Doctor, do pharmacists  
23 have any type of ethical obligations to  
24 the person whose medication they are

1     filling?

2             A.     Every professional has an  
3     ethical obligation.

4             Q.     Can you go over -- go ahead.

5             A.     It's part of the definition  
6     of being a professional.

7             Q.     Can you go through some of  
8     those ethical obligations with me that a  
9     pharmacist would have to a person who's  
10    filling their medication?

11            MS. KAPKE:   Object to form.

12            MS. THOMPSON:   Same  
13    objection.

14            THE WITNESS:   Following the  
15    laws, you know, being honest,  
16    accurate.   I'm not sure what  
17    you're getting at.

18    BY MR. VAUGHN:

19            Q.     Is informed consent part of  
20    the relationship a pharmacist has with a  
21    patient?

22            MS. THOMPSON:   Objection.  
23    Form.

24            THE WITNESS:   In my

1 professional career, informed  
2 consent is a document in a  
3 clinical trial that a patient  
4 signs that they understand and  
5 have been aware of the risks and  
6 the benefits of being involved in  
7 that clinical trial.

8 So I don't -- I don't see  
9 informed consent in what my daily  
10 practice was, in that term.

11 BY MR. VAUGHN:

12 Q. Is that because you don't  
13 actually fill medications for patients?

14 A. I wouldn't say it's for that  
15 reason. That's just not how informed  
16 consent is used.

17 Q. Do you not discuss informed  
18 consent at all with your pharmacy  
19 students?

20 A. In courses where I've taught  
21 the process of conducting clinical trials  
22 I have.

23 Q. If a pharmacist is aware  
24 that one medication contains a carcinogen

1 and another version of that same  
2 medication does not contain a carcinogen,  
3 should they warn the patient about that?

4 MS. KAPKE: Object to form.

5 THE WITNESS: I mean, again,  
6 in your hypothetical, you're  
7 supposing that they know this.  
8 And so if someone were to ask me  
9 or you in your former practice --  
10 you said you were a nurse?

11 BY MR. VAUGHN:

12 Q. Correct.

13 A. In your hypothetical that  
14 you had two compounds, one that was a  
15 known carcinogen, which is not what we're  
16 talking about here, and one that was, and  
17 one that wasn't, you know, would you go  
18 ahead and give them the one that was? I  
19 mean, I don't think anybody would answer  
20 that they would do that.

21 Q. What about probable  
22 carcinogen?

23 MS. THOMPSON: Objection to  
24 form.

1 THE WITNESS: You know, I  
2 don't -- I don't know that that  
3 changes.

4 I think I would have to look  
5 at the data to see if I agreed  
6 with it.

7 BY MR. VAUGHN:

8 Q. What if a top cancer  
9 researcher is the one that thinks that  
10 the levels are high enough to increase  
11 someone's risk of cancer?

12 Would you as a pharmacist  
13 defer to a top cancer researcher?

14 MS. THOMPSON: Objection.  
15 Form.

16 THE WITNESS: Again, I  
17 haven't practiced in a drug store  
18 setting in over probably 35 years.  
19 So I don't know how that  
20 information, if it were available,  
21 would actually reach the  
22 individual everyday practicing  
23 pharmacist.

24 BY MR. VAUGHN:

1 Q. So you don't know if there's  
2 a computer system that, like, notifies  
3 the pharmacist, hey, this drug has a  
4 carcinogen in it?

5 MS. KAPKE: Object to form.

6 THE WITNESS: Sorry. I'm  
7 pretty sure that's not the case.

8 BY MR. VAUGHN:

9 Q. Okay. If you were aware of  
10 literature that said the amount of a  
11 carcinogen in a medication would increase  
12 the risk of someone developing cancer,  
13 would you let the patient know that?

14 MS. KAPKE: Object to form.

15 MS. THOMPSON: Same  
16 objection.

17 THE WITNESS: Well, it's not  
18 done at that level where that  
19 responsibility is put in the hands  
20 of an individual practicing  
21 pharmacist.

22 Those decisions get made at  
23 corporate levels or at regulatory  
24 levels, not at the -- not at the

1 level of an individual practicing  
2 pharmacist.

3 BY MR. VAUGHN:

4 Q. What do you mean by  
5 corporate level?

6 A. Well --

7 MS. KAPKE: Sorry, Doctor.  
8 This is Kara Kapke again. I'm  
9 just going to interpose an  
10 objection to this entire line of  
11 questioning. This witness has  
12 been designated on general  
13 causation issues, not liability  
14 issues.

15 And there's been an  
16 agreement that the experts at this  
17 stage of the litigation are only  
18 testifying and will only be  
19 questioned about liability  
20 issues -- or only about causation  
21 issues, and they will not be asked  
22 about for -- designated on  
23 liability issues.

24 And so I think this entire

1 line of questioning is improper  
2 and in violation of the agreement  
3 that has been made and -- among  
4 the plaintiff and defendants.

5 MR. VAUGHN: I note your  
6 objection. And just for the  
7 record I'm trying to fully explore  
8 the opinions that are within his  
9 expert report.

10 Tyler, can we go back to his  
11 expert report, I guess. Let's go  
12 to Page 21.

13 MS. THOMPSON: And on that  
14 line, I mean, if you're going to  
15 talk about specific items in his  
16 report, that's fine. But I don't  
17 think anything about the ethical  
18 obligations of a dispensing  
19 pharmacist is in the report.

20 MR. VAUGHN: That's fine.

21 BY MR. VAUGHN:

22 Q. Here in the bottom of that  
23 first paragraph, you note the risks --  
24 you need to balance the risks and



1     benefits, that being the cornerstone --

2                     MR. VAUGHN:    Sorry, one  
3                     above that, Tyler.   Yeah, the very  
4                     last sentence there.

5     BY MR. VAUGHN:

6                     Q.       "The balance of risk/benefit  
7                     is the cornerstone of therapeutic  
8                     decisionmaking."

9                     That sounded a whole lot  
10                    like -- to me like informed consent.

11                    Does that not sound like  
12                    informed consent to you, Doctor?

13                    MS. THOMPSON:   Objection.  
14                    Form.

15                    THE WITNESS:    No.   As I said  
16                    before, informed consent is -- in  
17                    my professional experience, has  
18                    been used in the context of  
19                    enrolling a patient in a clinical  
20                    trial where there's a consent form  
21                    that they're asked -- that has to  
22                    be approved by an investigational  
23                    review board.

24                    And that's -- I'm not sure

1           that we're using the same  
2           terminology on what informed  
3           consent is.

4   BY MR. VAUGHN:

5           Q.     Okay. And so that informed  
6           consent that you're talking about in a  
7           clinical trial, what all does it have to  
8           disclose?

9           A.     The procedures of the study,  
10          the amount that they're being reimbursed  
11          for participating in the trial, the  
12          nature of the drug, whether it's  
13          experimental or not, those kind of  
14          things.

15          Q.     What does that have to --  
16          this says decisionmaking, though, in your  
17          opinion. What does what you just said  
18          have to do with decisionmaking?

19          A.     It doesn't. That's why I  
20          was saying the use of the term "informed  
21          consent" is not what this is.

22          Q.     Okay. So you don't think  
23          that a patient needs to be aware of all  
24          risks and all benefits in order to obtain

1 informed consent?

2 MS. KAPKE: Object to form.

3 MS. THOMPSON: Object to  
4 form.

5 THE WITNESS: Again,  
6 therapeutic decisionmaking is  
7 different from informed consent.  
8 So I think that you're using it in  
9 a context that it's not typically  
10 used in.

11 BY MR. VAUGHN:

12 Q. Okay. So for therapeutic  
13 decisionmaking when we're talking about  
14 the risk and the benefit, would one of  
15 the risks be what the level of NDMA is in  
16 a pill?

17 A. I think you would have to  
18 assess that risk and decide if there was  
19 one or not.

20 Q. What other risk -- when  
21 taking valsartan, besides how much of a  
22 carcinogen in it, what are the other  
23 risks that would go into this therapeutic  
24 decisionmaking?

1           A.       Well, first let me -- let me  
2       say that using the term "carcinogen"  
3       is -- it's a probable carcinogen in  
4       humans. We don't have the data that it's  
5       a for sure carcinogen.

6                       Drugs have all kinds of  
7       risks, particularly sartans.  
8       Hyperkalemia, hypotension, renal  
9       dysfunction. So the -- a rare case of  
10      angioedema.

11                      Those are the kind of risks  
12      that you typically consider when you're  
13      talking about therapeutic decisionmaking.

14           Q.       Of those potential  
15      complications that you just listed, would  
16      you consider any of those or the  
17      development of cancer to be a bigger risk  
18      to the patient?

19                      MS. THOMPSON:   Objection.  
20                      Form.

21                      THE WITNESS:   Well, if the  
22      question is, is cancer worse than  
23      hyperkalemia, then I would say  
24      yes, it is.

1 BY MR. VAUGHN:

2 Q. And so would it not be very  
3 important to know the levels of a  
4 potential carcinogen in a medication and  
5 evaluating the risk/benefit of that  
6 medication?

7 MS. THOMPSON: Objection.

8 MS. KAPKE: Object to form.

9 THE WITNESS: Yeah, again, I  
10 think we're getting back into this  
11 liability issue that is not what I  
12 was considering.

13 I was looking at the  
14 metabolism and distribution of  
15 NDMA and NDEA.

16 And by putting this comment  
17 in my statement or in my report,  
18 it was more to remind people that  
19 when the risk is unknown, which is  
20 what I consider it to be, unknown  
21 in humans, you also have to  
22 remember stopping drugs in  
23 patients is not without risk as  
24 well.

1 And that's been clearly  
2 identified in all of the FDA  
3 reports that I've seen.

4 BY MR. VAUGHN:

5 Q. Doctor, why are there no  
6 studies of NDMA in humans?

7 A. Why are there no studies?

8 Q. Yeah.

9 A. I'm not sure.

10 Q. Would it be ethical to give  
11 humans NDMA and study what happens?

12 MS. THOMPSON: Objection.  
13 Form. Outside the scope.

14 THE WITNESS: I think it  
15 depends on the amount.

16 BY MR. VAUGHN:

17 Q. So you think the regulatory  
18 agencies would approve a study on a  
19 probable carcinogen in humans?

20 MS. THOMPSON: Objection to  
21 form. Outside the scope.

22 THE WITNESS: Yeah, I don't  
23 know. I think it would depend on  
24 the amount, but I don't know.

1 BY MR. VAUGHN:

2 Q. Okay. So in forming your  
3 opinions, you did not consider any human  
4 data regarding NDMA exposure, correct?

5 A. That is not correct.

6 Q. I thought you said that  
7 there wasn't any.

8 A. I think what I said is that  
9 there were no data in humans showing that  
10 it was a carcinogen. Or --

11 Q. What's -- go ahead.

12 A. I'm sorry. Or proving that  
13 it was a carcinogen.

14 Q. Okay. What studies did you  
15 look at in humans then that you are  
16 opining didn't show it can cause cancer?  
17 Because I didn't see that in your expert  
18 report.

19 A. Let's go to Pages 48 through  
20 end of 55, 56.

21 I did review the  
22 epidemiology studies that have been done.

23 Q. Okay.

24 A. Either environmental or

1 dietary.

2 And let me be clear about  
3 what my reason for putting that in my  
4 report was.

5 I wasn't attempting to  
6 individually critique or support any one  
7 of these studies.

8 The purpose of putting them  
9 in my report is that I saw some plaintiff  
10 experts that looked at these same data  
11 and were pretty confident in stating that  
12 this proves that NDMA causes cancer.

13 And I look at the same  
14 data -- and again, without getting into  
15 discussion of odds ratios and confidence  
16 limits, I didn't see a consistency in  
17 these data that led me to the same  
18 conclusion.

19 And so I thought it was  
20 worth putting in my report that two  
21 people or more looking at these same data  
22 might not necessarily draw the exact same  
23 conclusion.

24 Q. Would you agree that these



1 studies in humans at least identify what  
2 organs NDMA could impact, if it went  
3 systemically?

4 MS. THOMPSON: Objection.  
5 Form.

6 THE WITNESS: I don't think  
7 so. Because I don't think this  
8 proves anything.

9 BY MR. VAUGHN:

10 Q. Why?

11 A. Because of their  
12 inconsistency, some of their limitations  
13 that, again, that others have commented  
14 on. You know, if this proved that it was  
15 definitely a human causing cancer  
16 substance, then it would have had a  
17 different level of designation in the  
18 IARC.

19 Q. When you say prove, what  
20 level of evidence is that? Is that like  
21 more likely than not, like 51 percent,  
22 75 percent? Do you have to get to  
23 100 percent to get to prove?

24 A. I don't know. I don't have

1 an opinion on that level.

2 My comment more is that  
3 there's inconsistency in the data. And  
4 so I don't know what that cut point ought  
5 to be.

6 Q. So is it your opinion that  
7 every single study must say that NDMA  
8 causes cancer in order to prove that it  
9 causes cancer?

10 MS. THOMPSON: Objection.  
11 Form. Mischaracterizes.

12 THE WITNESS: Yeah, that's  
13 not what I'm saying.

14 What I'm saying is these  
15 data look inconsistent enough to  
16 me that I would not be willing to  
17 draw the conclusion that we have  
18 proof that NDMA causes cancer in  
19 humans based on these epidemiology  
20 trials and their limitations and  
21 their inconsistencies.

22 MR. VAUGHN: We've been  
23 going for a little over an hour.  
24 Now is a decent time for a break

1 if you guys want to take one.

2 MS. THOMPSON: That's fine  
3 with us.

4 MR. VAUGHN: All right.  
5 Want to do --

6 THE VIDEOGRAPHER: The time  
7 right now is 10:06 a.m. We're off  
8 the record.

9 (Short break.)

10 THE VIDEOGRAPHER: The time  
11 right now is 10:20 a.m. We're  
12 back on the record.

13 BY MR. VAUGHN:

14 Q. Doctor, do you have any  
15 programs open on your computer except for  
16 Zoom?

17 A. No.

18 Q. And you'll keep it that way  
19 for the whole deposition?

20 A. Yes.

21 Q. Great. A second ago you  
22 said human studies did not prove that  
23 NDMA causes cancer in humans. Doctor, do  
24 you agree, though, that at least some of

1 the studies in humans where they gave  
2 them NDMA or where they were exposed to  
3 NDMA, that they found an association  
4 between increasing levels of NDMA and  
5 increasing rates of cancer?

6 MS. THOMPSON: Objection.  
7 Form.

8 THE WITNESS: Yes, some of  
9 those studies did show a  
10 statistical association.

11 BY MR. VAUGHN:

12 Q. And was that cancer that  
13 they found an association with NDMA, was  
14 that specific to a certain organ?

15 A. No.

16 Q. What organs do you recall  
17 being associated with NDMA being able to  
18 incite cancer?

19 MS. THOMPSON: Objection.  
20 Form.

21 THE WITNESS: Well, again,  
22 the association was in differing  
23 studies, different organs. They  
24 looked at almost anything that you

1           can imagine. So it's sort of all  
2           over the board.

3       BY MR. VAUGHN:

4           Q.       There's a lot of organs that  
5       NDMA is associated with causing cancer in  
6       these studies?

7           A.       There were many different  
8       organs, yes. Again, I would add that it  
9       wasn't necessarily within an individual  
10      organ that it was always consistent that  
11      it did show the association.

12          Q.       Doctor, your audio cut out  
13      again.

14          A.       I'm sorry. What I was  
15      adding was that in many cases when you  
16      looked at a specific organ, for example,  
17      you might find inconsistent results that  
18      one study would find an association and  
19      another study would not.

20          Q.       Doctor, how many hours did  
21      you spend in coming to your opinions  
22      within your expert report?

23          A.       I'd have to look at the two  
24      invoices that I have sent. I'm guessing

1 somewhere around 100 to 120, something  
2 like that.

3 MR. VAUGHN: Tyler, can we  
4 go back to Exhibit B of his expert  
5 report.

6 And can we go to the next  
7 page.

8 BY MR. VAUGHN:

9 Q. Doctor, can you read off the  
10 names of all plaintiff expert reports  
11 that you reviewed?

12 A. Not off the top of my head,  
13 but I certainly did review these that you  
14 see on my list.

15 MS. THOMPSON: Here is the  
16 same thing in hardcopy. Sorry.  
17 It might be easier to read.

18 THE WITNESS: Yeah, so the  
19 ones that you see here, are the  
20 ones that I did look at.

21 BY MR. VAUGHN:

22 Q. Can you go ahead and read  
23 those off for me, aloud?

24 A. Etminan, Panigrahy, Hecht,

1 Lagana, Madigan.

2 Q. And then at the top of that  
3 it says with exhibits. What does that  
4 mean? Does that mean like their CV and  
5 their materials considered?

6 A. CVs, not thoroughly, but  
7 just to get an idea of what their  
8 background was and where -- what  
9 institutions they were in.

10 And in reading the report,  
11 if there was a material that I thought  
12 was germane to what I was doing, that I  
13 might have looked at those too.

14 Q. Did you consider the  
15 experts' CV when you were critiquing  
16 their opinions?

17 A. In terms of their background  
18 or their institution they were in, or  
19 what part of the CV?

20 Q. Any part of the CV?

21 A. No. No that was not apart  
22 of my critique is what their CV would  
23 have been.

24 Q. I'm not saying critiquing

1     their CV. I'm saying when you were  
2     critiquing their opinions, did you  
3     consider what their specialty and  
4     background was?

5             A. I mean, yes, I would have  
6     considered it. I don't think it played  
7     any role in what my critique was though.

8             Q. Okay. Did you review the  
9     literature that each plaintiff expert  
10    relied on?

11            A. Not all.

12            Q. Approximately how much of it  
13    did you review?

14            A. I think it might have  
15    depended on who it was, but I relied  
16    mostly on their report and not on the  
17    materials that they used to derive their  
18    report.

19                    So 20 percent, if I felt it  
20    was germane to what I was interested in.

21            Q. But you didn't consider all  
22    of the citations that plaintiffs' experts  
23    used to support their opinions?

24                    MS. THOMPSON: Objection.



1 Form.

2 THE WITNESS: No, I did not.

3 BY MR. VAUGHN:

4 Q. Was there one expert report  
5 that you focused on more than the others?

6 MS. THOMPSON: Objection.

7 Form.

8 THE WITNESS: No, not  
9 really. I sort of gave them equal  
10 weight and time relative to how  
11 big they were and how detailed  
12 they were.

13 BY MR. VAUGHN:

14 Q. Do you recall which one was  
15 the largest expert report?

16 A. Not exactly. My best  
17 recollection was Panigrahy, but I can't  
18 swear to that.

19 Q. Do you recall approximately  
20 how many pieces of literature  
21 Dr. Panigrahy relied on?

22 A. I don't recall at all.

23 Q. So you don't know if it was  
24 100, 200, 500 articles?

1 A. I do not.

2 Q. If you reviewed the article  
3 that a plaintiffs expert relied on, would  
4 that appear on your materials considered  
5 list?

6 MS. THOMPSON: Objection.

7 Form.

8 THE WITNESS: If it was  
9 included in the exhibits, which is  
10 what this says is my reliance  
11 document, then I would have had  
12 it.

13 BY MR. VAUGHN:

14 Q. Well, if the exhibit just  
15 gave the names of the studies and didn't  
16 actually have the study itself there, did  
17 you go and find that study to look at?

18 A. If there was a study I had  
19 interest in, I wouldn't have had any  
20 assessment on it based on just reading  
21 the title of the study. I would have  
22 pulled the study if I felt like I needed  
23 to look in.

24 Q. And then would that -- would

1     you have then included that on your  
2     materials considered list in the area  
3     that lists all the different studies that  
4     you reviewed?

5             A.     Not always.

6             Q.     Why not?

7             A.     If it ended up not being  
8     something that was used to form my  
9     opinions, then I didn't feel it was  
10    relevant to put in my reliance list.

11            Q.     And so you didn't even  
12    critique the literature that plaintiffs'  
13    experts relied on? It just wasn't  
14    relevant to you?

15            MS. THOMPSON: Objection to  
16    form. Mischaracterizes.

17            THE WITNESS: Yeah, I didn't  
18    say it was irrelevant.

19            When I looked at them, I  
20    would have decided if it was  
21    relevant or irrelevant to what I  
22    was doing.

23    BY MR. VAUGHN:

24            Q.     Okay. How many deposition

1 transcripts with exhibits did you review  
2 in forming your opinions?

3 A. The ones that are listed  
4 here.

5 Q. And were each of those  
6 transcripts several hundred pages?

7 A. Yes.

8 Q. Who is this Daniel Barreto?  
9 I don't know if I'm saying the names  
10 right.

11 A. I have to look at my notes.  
12 He might have been a Teva employee.

13 Q. Do you know what any of  
14 these depositions you reviewed -- can you  
15 tell me who any of them are or who they  
16 work for?

17 A. The one that I remember the  
18 most because it -- was Nudelman. I know  
19 he was a Teva employee involved in sort  
20 of risk assessment or something like  
21 that.

22 Q. Why did you -- why were  
23 these the transcripts you decided to  
24 review out of all the depositions that

1 have been taken in this litigation?

2 A. These were the ones that I  
3 received from counsel.

4 Q. So counsel determined what  
5 you reviewed?

6 MS. THOMPSON: Objection.

7 Form. Mischaracterizes.

8 THE WITNESS: No. Counsel  
9 does not determine what I review.

10 BY MR. VAUGHN:

11 Q. Did you ask to review  
12 certain depositions of people in certain  
13 positions?

14 A. No.

15 MR. VAUGHN: All right. Can  
16 we scroll down a little bit,  
17 Tyler, on this regulatory guidance  
18 and documents.

19 BY MR. VAUGHN:

20 Q. I note there's over 40  
21 regulatory guidances and documents on  
22 your materials considered. How did you  
23 come into possession of all of these  
24 regulatory guidelines?

1 A. Where are we now?

2 Q. Bottom of the page. So it  
3 starts -- bottom of Page 1, and I think  
4 it goes to -- two, three -- yeah, till  
5 Page 3 is your regulatory guidance  
6 documents.

7 A. I'd say some of them came  
8 from counsel as part of what were called  
9 my initial documents for consideration.  
10 And some of them were documents that I  
11 already had because in the nature of my  
12 normal day-to-day job responsibilities,  
13 as I try to keep track of what's going on  
14 with the drugs that I have an interest  
15 in.

16 So particularly, the FDA  
17 documents, most of those I had already.

18 Q. So you reviewed all these  
19 guidance documents, correct?

20 A. Yes.

21 Q. Did you have -- did you have  
22 any disagreements with any of these  
23 guidance documents?

24 A. I mean, how many did you say

1     there were?

2             Q.     About 40.

3             A.     Yeah, I can't recall  
4     specifically if I would have had an  
5     agreement within one or, you know, out of  
6     all the things it would have been in all  
7     the -- each of the individual 40  
8     documents. So I don't recall that  
9     specifically.

10            Q.     If you disagreed with the  
11     regulatory guideline, would that be not  
12     significant?

13                   MS. THOMPSON: Object to  
14     form.

15                   THE WITNESS: I don't know  
16     what significant would mean.

17     BY MR. VAUGHN:

18            Q.     I mean, would you not note  
19     it in your expert report if you disagreed  
20     with one of the regulatory guidance  
21     documents?

22            A.     Only, I suspect -- because I  
23     don't recall doing it. But only if I  
24     suspect it would have altered one of my

1 opinions.

2 Q. Do you know if any of these  
3 regulatory guidance documents lay out the  
4 methodology in which you -- and how you  
5 convert animal exposure to NDMA to human  
6 exposure?

7 MS. THOMPSON: Objection.

8 Form.

9 THE WITNESS: There may have  
10 been areas that touched on that in  
11 some of these documents. But I  
12 don't recall specifically which  
13 ones and where.

14 BY MR. VAUGHN:

15 Q. Would you agree that would  
16 be important for your methodology to  
17 follow what is laid out in the regulatory  
18 guidelines?

19 MS. THOMPSON: Objection.

20 Form.

21 THE WITNESS: In terms of  
22 forming my opinion on the  
23 distribution and metabolism of  
24 NDMA and NDEA?



1 BY MR. VAUGHN:

2 Q. On the equivalent dose for a  
3 human based on what an animal got.

4 A. Well, that question  
5 specifically has been addressed, not just  
6 in regulatory documents, but in many,  
7 many, many of the articles that I  
8 reviewed in the animal studies.

9 And I don't recall ever  
10 seeing a single one that did not list  
11 that as a limitation in expanding animal  
12 data to humans in this regard.

13 Q. Did you give more weight to  
14 an article or to a regulatory guidance?

15 A. I guess I don't look at it  
16 in those terms, to say one is better than  
17 the other or stronger than the other.

18 I would say that in general,  
19 regulatory documents look at a variety of  
20 clinical and/or animal situation or data  
21 as opposed to one single study.

22 So in a pure volume  
23 standpoint, there would probably be more  
24 data reviewed in a regulatory document.

1 But that's not always the case.

2 Q. If the regulatory document  
3 laid out a different methodology than  
4 some random study, which would you use?

5 MS. THOMPSON: Objection.  
6 Form.

7 THE WITNESS: Which would I  
8 use to do what with?

9 BY MR. VAUGHN:

10 Q. To convert the dose of NDMA  
11 given to an animal, to the equivalent  
12 dose needed to give a human.

13 A. Well, again, I'm not sure  
14 exactly what you're asking. So maybe you  
15 can rephrase it, and I'll try to do a  
16 better job of answering.

17 Q. No. It was a bad question.  
18 You're okay. We'll get to it here in a  
19 little bit.

20 A. Okay.

21 Q. Did you conduct your own  
22 literature review in forming your  
23 opinions?

24 A. Yes.

1           Q.     Can you explain your  
2 methodology on your literature review to  
3 me?

4           A.     Yeah. I'd be happy to.  
5                   Original communications  
6 between counsel and myself, I was asked  
7 to evaluate the metabolism and  
8 distribution of NDMA and NDEA. And then  
9 with a focus of -- in regards to the  
10 amount that had been identified in the  
11 valsartan tablets.

12                   And so after my original  
13 review of documents that were provided in  
14 those initial files, one of those was  
15 also the pleadings from plaintiffs.

16                   And even before I did my  
17 literature search, I went through those  
18 and tried to identify areas that were  
19 within my area of expertise, like  
20 bioequivalence, drug metabolism, and  
21 those types of things. So I sort of knew  
22 what direction I was wanting to head.

23                   And then I went to PubMed  
24 and started looking at articles relative

1 to NDMA and NDEA and metabolism,  
2 dose-response, drug distribution.

3 And then, in addition, I  
4 looked at valsartan as well, just because  
5 there seemed to be issues about whether  
6 there was potential overlapping  
7 metabolism between valsartan and the  
8 impurity.

9 So I included valsartan,  
10 which pretty well characterized it, so it  
11 didn't take too long anything that I  
12 needed to find out about valsartan.

13 MR. VAUGHN: Tyler, can we  
14 go to the next page of this  
15 reliance list, or materials  
16 considered. One more page.  
17 Sorry.

18 BY MR. VAUGHN:

19 Q. At the bottom -- yeah, so  
20 literature and standards down here. I  
21 note that you have approximately 100,  
22 117 pieces of literature on here. Were  
23 you saying earlier that there's even more  
24 literature than this that you reviewed,

1     you just didn't include it on your  
2     materials considered?

3             A.     Yeah. I think there's more.  
4     Sometimes I would look at an article that  
5     I thought was relevant. And then one of  
6     my additional things that I do, instead  
7     of just relying on my PubMed returns, is  
8     I look at the references that are in that  
9     article.

10             And sometimes you find one  
11     that you might not have found through a  
12     PubMed search. And I decide whether that  
13     adds additional information or is  
14     supportive or -- so, yeah, there's other  
15     articles beyond these that, in the course  
16     of the last four or five months, that I  
17     looked at as well.

18             Q.     I mean, if you had to  
19     estimate, how many more? Like twice as  
20     many, another dozen?

21             MS. THOMPSON: Objection.  
22             Form.

23             THE WITNESS: I really can't  
24     give you a number. It could be

1           between 25 and 75. I don't really  
2           recall.

3       BY MR. VAUGHN:

4           Q.     So less than 200 articles in  
5           total you reviewed then?

6           A.     Maybe. It could be more  
7           than that.

8           Q.     So you reviewed five expert  
9           reports with the exhibits, eight  
10          deposition transcripts with exhibits,  
11          over 40 regulatory documents, and  
12          approximately 200 pieces of literature  
13          and 100 or so internal documents, and you  
14          did all of that in 100 to 120 hours; is  
15          that correct?

16          A.     That is correct.

17          Q.     Doctor, is this litigation  
18          the first time that you ever researched  
19          the carcinogenicity and potency of a  
20          probable human carcinogen?

21                       MS. THOMPSON: Objection.  
22                       Form.

23                       THE WITNESS: Probably the  
24                       first time to this level of

1 research. But the concepts here  
2 are essentially the same for any  
3 new drug or any grant that I  
4 submitted, where you have to be  
5 thorough in your approach to  
6 evaluating the literature,  
7 selecting that, that you think is  
8 relevant to what your question is  
9 that you're trying to answer.

10 And so I -- it's maybe the  
11 second time that I've looked at  
12 what would be a potential  
13 carcinogenic response to a drug.  
14 But it's not any different from  
15 what I've done for the last  
16 35 years.

17 BY MR. VAUGHN:

18 Q. I know you don't believe  
19 NDMA or NDEA to be human carcinogens.  
20 But would you agree with me that they are  
21 animal carcinogens?

22 MS. THOMPSON: Objection.  
23 Form.

24 THE WITNESS: Yes. There

1           are numerous, numerous studies  
2           showing carcinogenicity in  
3           animals.

4   BY MR. VAUGHN:

5           Q.     Are you aware of any animal  
6           that NDMA is not a carcinogen in?

7           A.     I didn't approach it looking  
8           for one that escaped that. So I don't  
9           know. I'm not aware of any, I don't  
10          know.

11          Q.     So you didn't consider if  
12          every mammal ever tested with NDMA was  
13          found to -- scratch that. Let me re-ask  
14          the question.

15                 So you didn't consider if  
16          every animal is susceptible to cancer  
17          formation when exposed to NDMA?

18          A.     There's no opinion in my  
19          report that was based on that, so no.

20          Q.     Is a human an animal?

21          A.     Yes.

22          Q.     I'm sorry. For the jury.

23                 So if every animal -- ever  
24          mammal tested with NDMA was found to



1 increase their risk of cancer, would that  
2 not be relevant to your opinion on if  
3 NDMA is a human carcinogen also?

4 MS. THOMPSON: Objection.  
5 Form.

6 THE WITNESS: No. And  
7 again, I don't differ from the --  
8 from the IARC's designation that  
9 this is a probable human  
10 carcinogen. I don't disagree with  
11 that assessment.

12 And as I said before, with  
13 the availability and the  
14 limitations of the epidemiology  
15 studies that have been done, those  
16 were available to IARC and they  
17 still didn't change that  
18 designation from probable.

19 So the number of animal  
20 species that had cancer responses  
21 to various, and I might add super  
22 high doses relative to what we are  
23 talking about with NDMA, that  
24 didn't change anything for me.

1 BY MR. VAUGHN:

2 Q. So at least in regards to  
3 animals, NDMA and NDEA are the most  
4 potent carcinogens that you've ever  
5 investigated, correct?

6 MS. THOMPSON: Objection.  
7 Form.

8 THE WITNESS: I mean,  
9 possibly, yes.

10 MR. VAUGHN: Tyler, can we  
11 go to Exhibit A of his expert  
12 report now.

13 I think this will be  
14 Exhibit 3 Tyler.

15 TRIAL TECH: Exhibit 3.  
16 Yes.

17 (Document marked for  
18 identification as Exhibit  
19 Bottorff-3.)

20 MR. VAUGHN: Thank you. Can  
21 we go to Page 11 of the PDF.  
22 Perfect.

23 BY MR. VAUGHN:

24 Q. Doctor. It looks like

1 you've been involved in many journals.  
2 What does it mean to be an editor of a  
3 journal?

4 A. When researchers write  
5 articles to be considered for  
6 publication, they first go to an editor.  
7 And the editor makes a preliminary  
8 decision about whether it's worthy or not  
9 of publication.

10 And if they believe it is  
11 and within the scope of what that journal  
12 focuses on, then they will send it out to  
13 individual reviewers to provide specific  
14 comments on all of the methodology and  
15 conclusions and statistics and so forth.

16 So the editor level is sort  
17 of one step above the individual journal  
18 article referees or reviewers.

19 Q. How do you become either a  
20 referee or an editor on a journal?

21 A. Usually those journals will  
22 call me. Often it's a journal that I've  
23 published in several times already. And  
24 based on your expertise and experience,

1 they will invite you to be an editor. So  
2 it's a selection, not something that you  
3 volunteer for.

4 Q. So being an editor on a  
5 journal is kind of a way of -- you've  
6 been recognized as one of the leaders in  
7 that area. Is that fair to say?

8 A. Very fair to say, correct.

9 Q. Have you ever worked --  
10 sorry.

11 Have you ever been an editor  
12 or reviewer or referee for a journal that  
13 has a focus on cancer?

14 A. No. My focus has been  
15 cardiovascular drugs, but again,  
16 everything within the realm of those  
17 drugs involving their pharmacology,  
18 pharmacokinetics, pharmacodynamics,  
19 safety, efficacy.

20 Q. So, you know, sometimes  
21 people publish in journals that's a  
22 little outside of the scope of what their  
23 article is on. Have you ever been  
24 involved in the peer review process of an

1 article on cancer, that was submitted for  
2 publication?

3 A. Gosh, you know, some of  
4 these were 25 to 30 years ago, so I don't  
5 recall. I know it wouldn't have been a  
6 major area of the articles that I would  
7 have been asked to review. But it's  
8 possible there was something there. And  
9 I didn't -- that I just don't recall.

10 MR. VAUGHN: Tyler, can we  
11 go to Page 3 of this document, PDF  
12 Page 3.

13 BY MR. VAUGHN:

14 Q. I see there's like 141  
15 invited presentations that you listed.

16 A. Is that all?

17 Q. Right. Can you explain to  
18 me what invited presentations are?

19 A. Anywhere from -- yeah,  
20 because those are followed by scientific  
21 presentations. So I've done about maybe  
22 1,500 internationally and nationally.

23 I break them down into two  
24 types. One would be if a professional

1 society, a local organization, a  
2 pharmacist, physicians, nurses would ask  
3 me to give a presentation, that would be  
4 an invited presentation in that setting.

5 The other ones that are more  
6 scientific are typically either  
7 professional societies or places like  
8 hospitals to do grand rounds and those  
9 types of things.

10 Q. Of all these invited  
11 presentations, of the 141 listed, do any  
12 of them relate to the carcinogenicity of  
13 a substance?

14 MS. THOMPSON: Object to  
15 form.

16 THE WITNESS: No, they all  
17 relate to the safety, efficacy,  
18 therapeutic decisionmaking, if you  
19 will, of cardiovascular drugs in  
20 general.

21 BY MR. VAUGHN:

22 Q. You're noting the different  
23 types of people -- or organizations that  
24 would invite you to give these

1 presentations. Would any of them be  
2 pharmaceutical companies?

3 A. No, I wouldn't have listed  
4 those. And they usually don't invite  
5 someone like me to just come in and give  
6 a presentation. I have done, in  
7 40 years, maybe three or four of those.  
8 But that's not a usual thing that  
9 happens.

10 Q. Have you ever given a  
11 presentation on behalf of a  
12 pharmaceutical company?

13 A. Yes. And that gets back to  
14 the speaker bureau question that we had  
15 earlier this morning.

16 Q. And they pay you for those  
17 presentations?

18 A. Correct. And these  
19 professionals societies, when they invite  
20 you, they pay you as well.

21 Q. But, again, some of the  
22 presentations that you've given, you were  
23 hired by a pharmaceutical company, but  
24 you weren't presenting to the

1 pharmaceutical company, correct?

2 A. Correct. I was presenting  
3 to other healthcare professionals.

4 Q. Do you disclose to them when  
5 you are presenting, that you're hired to  
6 present to them by the pharmaceutical  
7 company?

8 A. Yes. That's required.

9 Q. And then under the  
10 scientific presentations that you were  
11 also talking about, do any of them relate  
12 to the carcinogenicity of a substance?

13 A. No. I don't believe so.  
14 They're all related again to the complete  
15 profile and safety and efficacy and the  
16 therapeutic application of any  
17 cardiovascular drug that I had an  
18 interest in.

19 MR. VAUGHN: Tyler, can we  
20 go to PDF Page 10.

21 BY MR. VAUGHN:

22 Q. You list numerous awards  
23 spanning several decades. Do any of the  
24 awards have anything to do with cancer



1 research?

2 A. No. I don't do cancer  
3 research.

4 Q. Why don't you do cancer  
5 research?

6 A. My focus is on  
7 pharmacokinetics, pharmacodynamics, drug  
8 metabolism, drug interactions with  
9 cardiovascular drugs. And if cancer was  
10 part of that, then that's part of that.  
11 But --

12 Q. So in general, would you be  
13 relying in your professional field on  
14 someone who has a focus in cancer  
15 research?

16 MS. THOMPSON: Objection.  
17 Form.

18 THE WITNESS: Would I be  
19 relying on -- I'm sorry. I'm not  
20 sure I understand the question.

21 BY MR. VAUGHN:

22 Q. I guess -- so you said that  
23 you don't really research carcinogenicity  
24 of substances.

1                   If you needed to know the  
2     carcinogenicity of a substance in your  
3     daily practice, where would you get that  
4     information, would you defer -- would you  
5     get it from an expert in the field?

6                   MS. THOMPSON:   Objection.  
7     Form.   Mischaracterizes.

8                   THE WITNESS:   Yeah, I'm not  
9     sure under what circumstances that  
10    might be.   But yeah, I could --  
11    oncology people were part of the  
12    academic medical centers where I  
13    was.   So I could always have  
14    access to them.

15   BY MR. VAUGHN:

16                  Q.     All right.   You would agree  
17    that the oncologists at the places that  
18    you've worked at would be more qualified  
19    to give an opinion on the carcinogenicity  
20    of a substance than you?

21                  MS. THOMPSON:   Objection.  
22    Form.

23                  THE WITNESS:   Not if it came  
24    to the area of drug metabolism and

1 pharmacokinetics.

2 They would refer to me.

3 BY MR. VAUGHN:

4 Q. What about dose-response?

5 A. Pretty much the same thing  
6 in the context of how a drug is  
7 metabolized.

8 Q. Would you consult with them?

9 MS. THOMPSON: Objection.

10 Form.

11 THE WITNESS: If necessary.

12 MR. VAUGHN: All right. Can  
13 we go to PDF Page 12 now, Tyler.

14 BY MR. VAUGHN:

15 Q. Again, you have lots of  
16 committees that you've been on in your  
17 career.

18 Do any of them, of these  
19 committees, have a focus on cancer?

20 A. Again, I'm not trying to  
21 recall every single committee that I've  
22 been on, but I have been on, and chaired  
23 institutional review boards where  
24 cancer-related studies were part of the

1 submission. So I have interacted in  
2 that -- in that regard.

3 Q. Do you recall any of those  
4 cancer related studies that you just  
5 referenced?

6 A. Not off the top of my head,  
7 no.

8 Q. A long time ago?

9 A. I mean, in the range of 10  
10 to 20 years ago, yes.

11 Q. Has the field of  
12 pharmacology evolved in the last ten  
13 years?

14 MS. THOMPSON: Objection.  
15 Form.

16 THE WITNESS: Quite a bit.

17 BY MR. VAUGHN:

18 Q. What about cancer or our  
19 knowledge on carcinogens?

20 A. It looks like it has, based  
21 on some of the documents that I reviewed  
22 for this.

23 MR. VAUGHN: And, Tyler, can  
24 we go to PDF Page 14, please.

1 BY MR. VAUGHN:

2 Q. It looks like you have been  
3 37 grants or contracts. What is a grant  
4 or a contract?

5 A. A grant is typically  
6 something you submit to a funding agency.  
7 And they review and approve for funding.

8 A contract is more a  
9 negotiation with a funding agency,  
10 specifically for something that you want  
11 to do. And you're not necessarily in  
12 competition for other people like you  
13 would be for a grant.

14 Q. Are you doing animal studies  
15 here or just all different types of  
16 studies?

17 A. Majority is human  
18 pharmacokinetics, pharmacodynamics, and  
19 drug interactions.

20 I have done animal studies.  
21 I'm not sure I got funded for any of  
22 those. But I have worked in a fair  
23 number of animal studies.

24 Q. What experience do you have

1 with animal studies?

2 A. My earliest one is at the  
3 University of Kentucky as a resident.  
4 One of my projects was looking at drug  
5 distribution based on obesity using a rat  
6 model. These are called Zucker rats.

7 I was mostly just helping  
8 out in the lab and looking at the  
9 techniques. So I never became an author  
10 on the paper. But I have done that in  
11 animals.

12 I've also done a dog study  
13 looking at isolated cardiac myocytes in  
14 the lab. And I've done some did  
15 defibrillation threshold studies in pigs,  
16 which I do have publications on.

17 Q. Have you ever done any  
18 carcinogenicity studies in animals?

19 A. No.

20 Q. In your opinion, what animal  
21 or animals are most similar to a human in  
22 how they are going to respond to a drug?

23 A. It depends. And -- you  
24 know, when you're looking at a specific

1 drug metabolism, then what it appears --  
2 and this popped up in many of the studies  
3 that I looked at for my report -- that  
4 the rat is actually the animal that seems  
5 the most similar to humans for drug  
6 metabolism based on a standardized weight  
7 of the liver in the rat, versus the liver  
8 of a human, and not quite so much so in  
9 the other animal models of drug  
10 metabolism.

11 Q. So are you telling our jury  
12 that humans are more similar to rats than  
13 they are to monkeys?

14 MS. THOMPSON: Objection to  
15 form.

16 THE WITNESS: In terms of  
17 opposing thumbs, I think we're  
18 closer to monkeys. But in terms  
19 of drug metabolism, sometimes  
20 we're closer to rats.

21 BY MR. VAUGHN:

22 Q. What about our DNA? What  
23 percentage of our DNA do we share with  
24 monkeys? Do you know?

1 MS. THOMPSON: Objection.  
2 Scope.

3 THE WITNESS: I think it's  
4 probably in the 90 percent.  
5 Something like that.

6 BY MR. VAUGHN:

7 Q. What percent of DNA do we  
8 share with rats?

9 A. It's probably in the  
10 88 percent. So it's not as far off as  
11 you would think.

12 Q. But we're more similar, DNA,  
13 at least wise, to a monkey than a rat,  
14 correct?

15 MS. THOMPSON: Objection.  
16 Form.

17 MR. VAUGHN: I appreciate if  
18 you quit laughing, Counsel.

19 MS. THOMPSON: Sorry. This  
20 is a really funny line of  
21 questioning.

22 THE WITNESS: Again, I think  
23 it depends on what you are talking  
24 about. And for this litigation,



1           for the question that I was asked  
2           to address, it just turns out that  
3           drug metabolism of NDMA is more  
4           closely related in the rat than it  
5           would be in any of the other  
6           species.

7                       And that's not getting into  
8           the oncology part of it. It's  
9           just getting into the drug  
10          metabolism part. And that's the  
11          part where I focus.

12       BY MR. VAUGHN:

13               Q.     Are there any oral human  
14          studies of NDMA exposure?

15               A.     Other than the epidemiology  
16          ones that we've mentioned already?

17               Q.     Mm-hmm.

18               A.     I do believe there was a  
19          ranitidine study that looked at urinary  
20          NDMA. I didn't focus on it for this  
21          particular question that I was asked to  
22          address. But I think there is at least  
23          one that I can vaguely recall seeing.

24               Q.     And did it look into the

1 metabolism of NDMA in the human body?

2 A. Not that I recall. But  
3 again I didn't -- it's been a while since  
4 I saw that one. So I haven't considered  
5 it recently.

6 Q. What are you basing your  
7 opinion on that humans metabolize NDMA  
8 the same -- most similarly to rats of any  
9 animal?

10 A. Numerous mentions of that in  
11 the articles that I considered for this.  
12 And I'm trying to recall. I probably  
13 have in my note when it happened. If we  
14 want to take the time to do that, I can  
15 recall one specifically.

16 But my recollection is I saw  
17 that as many as four or five times  
18 mentioned.

19 Q. Did you look to see how they  
20 came to their opinion on that?

21 A. Again, in the absence of  
22 pharmacokinetic studies in humans, it was  
23 more based on either rat 2E1, which is  
24 the major metabolizing enzyme in question

1 here for NDMA, and NDEA for that matter.  
2 That was one area that was discussed.

3 And then another area was  
4 the volume that you can isolate of P450  
5 per gram of liver in the rat is similar  
6 if not close to identical to what you see  
7 with that same calculation in the human.

8 Q. Is P450 an important --  
9 strike that question.

10 What organs in the human  
11 body have P450?

12 A. Many. But in almost every  
13 study that I've ever seen, the majority,  
14 by an overwhelming majority is the liver.  
15 You do have, depending on the enzyme,  
16 some in the gut wall, like the upper  
17 small intestine, the kidney, the lungs.

18 There are a variety of other  
19 organs that have been identified to have  
20 it. But on a rank order, it's liver far  
21 and away number one, gut wall number two.

22 Q. And so would you agree with  
23 me that an organ or tissue must contain  
24 P450 in order for NDMA to be able to

1 incite cancer in that organ?

2 A. Yes. And that's been  
3 written about in numerous of the studies  
4 that I reviewed.

5 Q. And so you would also agree  
6 that organs with P450, if exposed to  
7 NDMA, could be susceptible to cancer  
8 formation?

9 A. Depending on the dose. And  
10 then depending on the amount of P450 in  
11 that organ, because they don't all have  
12 the same amount.

13 So if you give the same dose  
14 to two different organs and have one  
15 organ that has ten times the P450 of the  
16 other, and then it would produce a  
17 different amount of carcinogen at that  
18 point.

19 So it is relying on both the  
20 dose, the amount of P450, and technically  
21 in the way in which the drug is  
22 administered as well.

23 Q. But you're unable to tell me  
24 how much of a dose of NDMA is needed in a

1 human, right?

2 MS. THOMPSON: Object to  
3 form.

4 THE WITNESS: No one has  
5 that data.

6 Sorry.

7 BY MR. VAUGHN:

8 Q. These grants and contracts  
9 that you received, are any of them from  
10 pharmaceutical manufacturers?

11 A. Some of them are. Yes.

12 Q. What's the most recent grant  
13 or contract that you received, do you  
14 recall, or do you know?

15 A. I can tell you looking here.  
16 2013, which is around the  
17 time that I started switching my  
18 responsibilities from primarily a  
19 researcher clinician, educator, faculty  
20 member to picking up more administrative  
21 responsibilities.

22 Q. You are no longer conducting  
23 research, correct?

24 MS. THOMPSON: Objection.

1 Form.

2 THE WITNESS: Not in the way  
3 in which would be reflected in  
4 terms of doing, you know, a grant  
5 submission or something like that.

6 But again, you know,  
7 researching drugs, their  
8 pharmacology, that's almost a  
9 daily thing for me for 40 years.

10 MR. VAUGHN: And, Tyler, if  
11 we can go to PDF Page 15.

12 BY MR. VAUGHN:

13 Q. So your publications start  
14 there. And it looks like you have about  
15 50 publications listed. Do any of your  
16 publications focus on cancer?

17 A. No, none of my publications  
18 focused on cancer. But you can see that  
19 they are heavily involved in drug  
20 metabolism, drug pharmacokinetics, drug  
21 pharmacodynamics.

22 MR. VAUGHN: And, Tyler, can  
23 you go to 19.

24

1 BY MR. VAUGHN:

2 Q. At the bottom you list  
3 original research. What do you mean by  
4 original research?

5 A. I try to break down  
6 publications by either books or book  
7 chapters that I've authored compared to  
8 review articles, you know, which are sort  
9 of an overview of a particular drug or  
10 drug topic.

11 But then original research  
12 are the actual studies that I conducted,  
13 most of the time in collaboration with  
14 others, and then have those published.

15 Q. And of your original  
16 research, any of it relate to cancer?

17 A. No. Again, it's all on  
18 pretty much a drug pharmacokinetics, drug  
19 metabolism, drug interactions, and  
20 pharmacodynamics.

21 Q. All right. So, Doctor, I  
22 don't see anywhere within your CV  
23 anything on cancer.

24 Can you explain to our jury

1     why you believe that you are qualified to  
2     provide an opinion as to the potency of a  
3     carcinogen?

4                     MS. THOMPSON:   Objection.  
5                     Form.

6                     THE WITNESS:   Again, I don't  
7                     think that I'm claiming anything  
8                     involving potency in the way in  
9                     which I think of that term from a  
10                    pharmacodynamic standpoint.

11                    But again, the question that  
12                    I was asked to review was how was  
13                    NDMA and NDEA metabolized and  
14                    where would they go and what would  
15                    happened to them at these doses.

16                    And, you know, without  
17                    sounding flippant, metabolism of  
18                    compounds evolved long before we  
19                    put drugs in capsules and tablets.

20                    So whether the chemical is  
21                    NDMA and is going through  
22                    cytochrome P450, whether it's a  
23                    cardiovascular drug or  
24                    noncardiovascular drug, it's going



1 through cytochrome P450.

2 Those principles are  
3 identical, and in fact were  
4 originally for ingested compounds,  
5 long before we made capsules and  
6 tablets.

7 So P450 has been around for  
8 way longer than valsartan for  
9 instance.

10 BY MR. VAUGHN:

11 Q. What is your definition of  
12 potency?

13 A. Potency would typically be a  
14 dose-response curve where you give  
15 multiple doses and then characterize the  
16 dose-response curve of two different  
17 substances. And if there is a shift to  
18 the left or to the right, then one of  
19 those would be considered more potent  
20 than the other.

21 That's how potency is  
22 defined in drug pharmacology.

23 Q. As a pharmacist, do you  
24 think you are more qualified than a

1 cancer research specialist to opine on  
2 the potency of a carcinogen?

3 MS. KAPKE: Object to form.

4 MS. THOMPSON: Objection.

5 Form.

6 THE WITNESS: As a  
7 pharmacist, what I'm probably more  
8 qualified than anyone that I've  
9 read depositions or expert reports  
10 on, is to comment on drug  
11 metabolism and drug distribution,  
12 and a dose-response relationship  
13 to that pharmacokinetic  
14 distribution.

15 BY MR. VAUGHN:

16 Q. When that substance is a  
17 potential carcinogen, you still think  
18 that you're more qualified than a cancer  
19 research specialist?

20 MS. THOMPSON: Objection.

21 Form.

22 THE WITNESS: In the context  
23 of what I focused on about drug  
24 metabolism, absolutely.

1 BY MR. VAUGHN:

2 Q. Did you do research to see  
3 if, you know, any of the properties of  
4 NDMA would change the way it's  
5 metabolized in comparison to a  
6 pharmaceutical drug?

7 MS. THOMPSON: Objection.  
8 Form.

9 THE WITNESS: Yes, I did  
10 actually.

11 And again, many of my  
12 research and publications has  
13 centered on not just drug  
14 metabolism, but routes of drug  
15 metabolism as a way of predicting  
16 drug interactions.

17 And the number one cause of  
18 a drug interaction is having two  
19 co-administered compounds that  
20 compete for the same metabolic  
21 pathway.

22 And so one of my areas of  
23 review was to describe how  
24 valsartan is distributed and

1           metabolized, eliminated. And the  
2           same for NDMA and NDEA. And I  
3           think clearly demonstrated in my  
4           report, that there's no overlap at  
5           all, so there would be no  
6           expectation of any -- having any  
7           effect on each other because of  
8           not sharing routes of elimination.

9       BY MR. VAUGHN:

10           Q.       When you were determining  
11           the levels that were -- of NDMA that were  
12           given to animals, and you were trying to  
13           opine what level would be needed for a  
14           human to be equivalent, did you base that  
15           in part off of the weight of the human?

16                   MS. THOMPSON:   Objection.  
17           Form.

18                   THE WITNESS:   I mean, we can  
19           look at that section in my report.  
20           But the way in which I tried to  
21           do, with all its limitations, the  
22           extrapolation of the animal data,  
23           particularly rats, because I think  
24           they are the closest approximation

1 to humans, into human dose  
2 equivalence, then that was done on  
3 a milligram-per-kilogram basis.

4 So yes, it incorporated the  
5 weight differential between the  
6 two species, if you will, humans  
7 and animals.

8 BY MR. VAUGHN:

9 Q. As a pharmacist and, you  
10 know, the medications that you deal with,  
11 is that how you convert every medication?  
12 You do it the same way?

13 A. Convert from what to what?

14 MS. KAPKE: Object to form.

15 BY MR. VAUGHN:

16 Q. From an animal to a human?

17 A. Sometimes. I think it  
18 depends on what's been done. And  
19 sometimes they use body surface area.  
20 But the usual way it's done is on a  
21 milligram-per-kilogram basis.

22 Q. Usual way, but not always,  
23 right?

24 A. Usual way but not always.

1 Q. Is there any -- is there any  
2 medication you're aware of or substance  
3 where scaling for weight is  
4 inappropriate?

5 MS. THOMPSON: Objection.  
6 Form.

7 THE WITNESS: Off the top of  
8 my head, I can't say. I suspect  
9 that it could be there. But I  
10 can't say. I don't know off the  
11 top of my head.

12 BY MR. VAUGHN:

13 Q. What factors would make it  
14 inappropriate to scale based on weight?

15 MS. THOMPSON: Objection.  
16 Form.

17 THE WITNESS: Well, not  
18 having seen that done very much, I  
19 don't have -- I don't have an  
20 opinion on what that would be.

21 BY MR. VAUGHN:

22 Q. And so you didn't consider  
23 what factors might make scaling for  
24 weight when converting NDMA from an

1 animal to a human, you didn't consider  
2 what factors might make that  
3 inappropriate?

4 A. If I had ever seen in the  
5 articles that I did review any allusion  
6 to that, then I would have considered it.  
7 But I didn't see it anywhere.

8 Q. You didn't see it anywhere.  
9 But you would have considered though if  
10 you did see it?

11 A. I would have always  
12 considered it if I saw it.

13 Q. And would it have been in  
14 your report then if you saw that?

15 A. Yes.

16 MR. VAUGHN: Counsel, right  
17 now is another really good time  
18 for a break. I know we're about  
19 an hour.

20 (Whereupon a discussion was  
21 held off the record.)

22 THE VIDEOGRAPHER: The time  
23 right now is 11:11 a.m. We are  
24 off the record.

1 (Short break.)

2 THE VIDEOGRAPHER: The time  
3 right now is 11:26 a.m. We're  
4 back on the record.

5 MR. VAUGHN: All right.  
6 Tyler, can you pull the expert  
7 report back up for us. And let's  
8 go to Page 63 again.

9 BY MR. VAUGHN:

10 Q. Doctor, can you read that  
11 opinion of yours at the bottom, VIII?

12 A. Yes.

13 "It is my opinion that no  
14 scientific professional could credibly  
15 claim to a reasonable degree of  
16 scientific certainty that plaintiffs'  
17 cancer was caused by their treatment with  
18 any valsartan product contain trace  
19 levels of NDMA and NDEA impurities during  
20 the time period in question."

21 Q. Doctor, what do you consider  
22 trace levels?

23 A. The amounts that I consider  
24 to be trace in these valsartan products.



1 Q. And that was 20 micrograms  
2 or less, correct?

3 A. Correct.

4 Q. And you say any valsartan  
5 product. How could you give that opinion  
6 when you haven't even reviewed all of the  
7 testing data?

8 MS. THOMPSON: Objection.  
9 Form.

10 THE WITNESS: Any valsartan  
11 product that I evaluated.

12 BY MR. VAUGHN:

13 Q. Okay. So again, just less  
14 than the 20 micrograms is what your  
15 opinion is limited to?

16 MS. THOMPSON: Objection.  
17 Form.

18 THE WITNESS: Not really.

19 BY MR. VAUGHN:

20 Q. So would it be more accurate  
21 to say that any valsartan product that  
22 the FDA reviewed?

23 MS. THOMPSON: Objection.  
24 Form.

1 THE WITNESS: No. What I  
2 used to draw that conclusion in my  
3 report were the levels of exposure  
4 to NDMA and NDEA in the animal  
5 studies that provided  
6 dose-response relationships that  
7 appeared to confine, number one,  
8 doses of NDMA that would not leave  
9 the liver due to first-pass  
10 metabolism, and that also did not  
11 appear to cause cancer in  
12 predominately rats because they're  
13 the best model for this.

14 BY MR. VAUGHN:

15 Q. You're aware -- if you were  
16 aware that the NDMA or NDEA levels in  
17 generic valsartan were higher than what  
18 the FDA was aware of, is that something  
19 that you would have considered in forming  
20 your opinions?

21 MS. THOMPSON: Objection.  
22 Form.

23 THE WITNESS: If we go back  
24 to the ZHP, for instance, comment

1           that was earlier in my report of  
2           120 parts per million.

3   BY MR. VAUGHN:

4           Q.     Mm-hmm.

5           A.     That would correspond to  
6           only about twice as much as what the  
7           highest amount was in any of the products  
8           that I evaluated.

9                     And if you look at my tables  
10          on 35, 36, 37, 38, 39, we're still  
11          talking about hundreds to thousands times  
12          more that was shown to be safe in animals  
13          than the amount even in that 120 parts  
14          per billion -- or million that we talked  
15          about.

16          Q.     What if the levels were go  
17          even higher than 120 parts per million?

18          A.     I don't have that  
19          information, so I don't know what that  
20          would look like or how much that would  
21          be. It's not enough information for me  
22          to make an opinion on.

23          Q.     Defense counsel would have  
24          needed to provide that information to you

1 for you to provide an opinion on it,  
2 right?

3 MS. THOMPSON: Objection.  
4 Form.

5 THE WITNESS: Or the FDA or  
6 anybody else.

7 BY MR. VAUGHN:

8 Q. So in this opinion, when you  
9 say no scientific professional could  
10 credibly claim, what do you mean by that?

11 Is that more than just  
12 disagreeing with the other side. Are you  
13 drawing into question their integrity in  
14 making their opinions?

15 MS. THOMPSON: Objection.  
16 Form.

17 THE WITNESS: No, I didn't  
18 draw this conclusion based on  
19 their opinions.

20 I drew that conclusion based  
21 on my research into NDMA  
22 metabolism and the dose-response  
23 relationship that this seemed to  
24 be far below that was associated

1 with any cancer in the hundreds to  
2 thousands times lower.

3 BY MR. VAUGHN:

4 Q. Would you consider some of  
5 the plaintiffs' experts to be scientific  
6 professionals?

7 A. Within their field, yes.

8 Q. And did any of them make the  
9 claim to a reasonable degree of  
10 scientific certainty that a plaintiff's  
11 cancer could have been caused by their  
12 treatment with valsartan containing NDMA  
13 or NDEA?

14 A. I believe they made those  
15 claims. I'm not sure they had access to  
16 the data that I've provided and whether  
17 that would have changed their opinions or  
18 not.

19 Q. And do you think that you  
20 reviewed all of the data that they  
21 reviewed?

22 A. Much of the same.

23 Q. And so this -- this opinion  
24 is not directed to any specific

1 plaintiffs' expert?

2 A. No, it is not.

3 Q. And it's not directed at any  
4 of them, correct?

5 A. Correct.

6 Q. Did you review  
7 Dr. Panigrahy's CV? You said that you  
8 did, correct?

9 A. I probably scanned it to  
10 see, you know, what his background and  
11 training was and what his interests were  
12 and what his current position was.

13 Q. Can you tell our jury what  
14 you recall about Dr. Panigrahy's  
15 credentials?

16 A. The details of that, I don't  
17 have off the top of my head. I'd have to  
18 look at my materials.

19 Q. So you don't recall that  
20 Dr. Panigrahy was a medical -- is -- was  
21 a medical doctor and completed a surgical  
22 residency?

23 A. If I looked at it I would  
24 recall that.

1 Q. Do you recall if  
2 Dr. Panigrahy has taught both surgery and  
3 pathology at Harvard?

4 A. If that's what he did, I  
5 would have recalled it if I saw it.

6 Q. All right. Do you recall  
7 that Dr. Panigrahy has devoted almost his  
8 entire career to studying cancer?

9 A. That rings a bell, yes.

10 Q. Do you recall that  
11 Dr. Panigrahy has been an editor on  
12 journals such as Carcinogenesis,  
13 Neoplasia, Cancer Research, Clinical  
14 Cancer Research and Nature Reviews  
15 Cancer?

16 A. Not those details, I don't  
17 recall.

18 Q. All the journals that I just  
19 listed, they all deal with cancer,  
20 correct?

21 A. I don't remember each one of  
22 them. But I heard cancer a few times.  
23 So I'm guessing that's the case.

24 Q. Does Carcinogenesis, does

1 that relate to cancer?

2 A. Yes.

3 Q. What about Neoplasia?

4 A. Yes.

5 Q. Cancer Research?

6 A. Yes.

7 Q. Clinical Cancer Research?

8 A. Yes.

9 Q. And Nature Reviews Cancer?

10 A. Yes.

11 Q. And previously you testified  
12 that being an editor on a journal  
13 signifies that you were a higher level or  
14 respected individual in that field,  
15 correct?

16 A. I think I --

17 MS. THOMPSON: Objection to  
18 form.

19 THE WITNESS: Sorry.

20 I think I used the word  
21 "recognized."

22 BY MR. VAUGHN:

23 Q. Okay. So would you agree  
24 with me that Dr. Panigrahy -- or



1 Panigrahy is a recognized leader in the  
2 field of cancer?

3 MS. THOMPSON: Objection.  
4 Form.

5 THE WITNESS: He seems to  
6 be.

7 BY MR. VAUGHN:

8 Q. Are you familiar with the  
9 NIH?

10 A. Yes.

11 Q. Can you tell our jury what  
12 the NIH is?

13 A. It's a research arm of the  
14 federal government that conducts some of  
15 its own research and then funds external  
16 researchers who apply for grants.

17 Q. Have you ever received  
18 funding from the National Institute of  
19 Health?

20 A. I applied twice and did  
21 not -- I got approved, but my priority  
22 score wasn't high enough to receive the  
23 dollars.

24 Q. So they just don't hand that

1 out to anybody, those grants, do they?

2 A. No.

3 Q. Are you aware -- are you  
4 familiar with National Cancer Institute?

5 A. That's one of the branches  
6 of the National Institutes of Health.

7 Q. That was going to be my next  
8 question. Thank you.

9 And have ever received -- I  
10 guess you have not received funding from  
11 the National Cancer Institute either,  
12 because that's part of the National  
13 Institute of Health?

14 A. That's correct. I have  
15 received no NIH funding of any of their  
16 branches.

17 Q. Do you recall that  
18 Dr. Panigrahy has received funding both  
19 from the National Institute of Health and  
20 the National Cancer Institute to study  
21 cancer in -- on numerous occasions?

22 MS. THOMPSON: Object to  
23 form.

24 THE WITNESS: I don't

1 recall -- sorry.

2 I don't recall those  
3 details, but if they are in his  
4 CV, I'm sure he did.

5 BY MR. VAUGHN:

6 Q. So you don't recall that the  
7 first time that he received funding was  
8 back in 1998 for advanced training in  
9 surgical oncology with a focus in  
10 laboratory research?

11 MS. THOMPSON: Objection.  
12 Form.

13 THE WITNESS: I do not  
14 recall that specifically.

15 BY MR. VAUGHN:

16 Q. And do you recall if the  
17 National Institutes of Health and the  
18 National Cancer Institute is still  
19 funding Dr. Panigrahy to research cancer  
20 to this very day?

21 MS. THOMPSON: Objection.  
22 Form.

23 THE WITNESS: I do not  
24 recall that detail.

1 BY MR. VAUGHN:

2 Q. Do you think the National  
3 Institute of Health and the National  
4 Cancer Institute would still be funding  
5 Dr. Panigrahy's cancer research if they  
6 questioned his credibility?

7 MS. THOMPSON: Objection.  
8 Form.

9 THE WITNESS: They probably  
10 would not fund someone whose  
11 credibility that they questioned  
12 based on the research that they  
13 submitted for review.

14 BY MR. VAUGHN:

15 Q. Are you aware that  
16 Dr. Panigrahy, one of the top cancer  
17 researchers in the world, spent around  
18 1,400 hours researching and drafting his  
19 opinions in this case?

20 MS. THOMPSON: Objection.  
21 Form.

22 THE WITNESS: I don't have  
23 access to that information. So I  
24 could not have been aware of that.

1 BY MR. VAUGHN:

2 Q. And you spent approximately  
3 100 to 120 hours, right?

4 MS. THOMPSON: Objection.  
5 Form.

6 THE WITNESS: So far, yes.

7 BY MR. VAUGHN:

8 Q. Would that be about  
9 10 percent of the time that Dr. Panigrahy  
10 spent?

11 MS. THOMPSON: Objection.  
12 Form.

13 THE WITNESS: That's how  
14 that would be calculated, yes.

15 BY MR. VAUGHN:

16 Q. Doctor, are you familiar  
17 with the term bioavailability?

18 A. Yes.

19 Q. Can you explain to the jury  
20 what bioavailability means?

21 A. Bioavailability is the  
22 assessment of what percent of a drug  
23 that's taken actually reaches what we  
24 would call the systemic circulation,

1     which means you can measure it in the  
2     bloodstream.

3             Q.     When the substance is taken  
4     orally, what primarily impacts the  
5     substance's bioavailability?

6             A.     Well, it's a multi-step  
7     process. And so the first step in that  
8     is the actual release of the compound  
9     from, let's say the pill or tablet that  
10    was taken. And there are a lot of  
11    examples of pills that don't completely  
12    release constituents.

13            But once they are, they are  
14    typically absorbed in the small  
15    intestine. And there is a round,  
16    potentially, depending on the product, of  
17    drug metabolism that occurs across the  
18    small intestine.

19            And once absorbed there, it  
20    goes directly into the liver where it  
21    sees another round of potential  
22    metabolism. And only after exceeding  
23    those steps, would it then show up in the  
24    bloodstream to measure its

1 bioavailability.

2 Then that would be expressed  
3 as a percentage of the dose of that  
4 particular drug or chemical that you  
5 gave.

6 Q. Give me one -- I'm reading  
7 the realtime. My internet cut out a  
8 little bit, so I missed part of your  
9 answer. So just give me one second.

10 You said that a lot of drugs  
11 don't release their constituents. Can  
12 you explain that further to me?

13 A. Yeah. It just depends on  
14 the drug. It's been noted with a lot of  
15 sustained-release drugs, for instance,  
16 that they release the drug so slowly that  
17 sometimes the product gets past the site  
18 of absorption before all the drug in it  
19 gets released. And, therefore, you don't  
20 get as good as bioavailability as you  
21 might expect you would get.

22 Q. Valsartan, would all of the  
23 NDMA be released or would some of that  
24 pass with the valsartan as it's being

1 excreted?

2 MS. THOMPSON: Objection to  
3 form.

4 THE WITNESS: My suspicion  
5 is that it would be released from  
6 the dosage form, yes.

7 BY MR. VAUGHN:

8 Q. Your suspicion -- what do  
9 you base your suspicion on?

10 A. Well, that dosage form is  
11 the type that usually is pretty much  
12 completely dissolved into its individual  
13 components before or by the time it  
14 reaches the upper part of the small  
15 intestine.

16 Q. So this process that you've  
17 been talking about of what impacts the  
18 bioavailability of a drug that is orally  
19 ingested, is that known as first-pass  
20 metabolism?

21 A. Well, not necessarily. You  
22 can give an injectable into the muscle  
23 and measure bioavailability. And that  
24 would not be going through first pass.



1                   So first pass is more  
2     pertinent to oral administration.

3                   Q.     That's what my question was,  
4     is with oral administration, it's known  
5     as first pass?

6                   A.     Yes.

7                   Q.     And the organs you said that  
8     were primarily involved, which is  
9     stomach, small intestine, liver?

10                  A.     Not so much the stomach.  
11     Small intestine and liver.

12                  Q.     Okay. And you would never  
13     expect to see NDMA in the blood of a  
14     human, correct, because you believe that  
15     the liver should be able to handle all of  
16     it?

17                  A.     Well, let me -- let me  
18     qualify that by saying that at the  
19     amounts that were found in the -- of NDMA  
20     and NDEA in the valsartan tablets, I  
21     would not expect that to reach the  
22     systemic circulation at all based upon  
23     first-pass metabolism.

24                  Q.     If someone were to find it

1 in the blood, that means it got past the  
2 liver, right?

3 A. I think that would be, if  
4 the dose was high enough, possible.

5 Q. Well, regardless of the  
6 dose, if it was found in the blood, that  
7 means it got past the liver, right?

8 MS. THOMPSON: Objection.  
9 Form.

10 THE WITNESS: Not  
11 necessarily. It could have gotten  
12 there from another source.

13 BY MR. VAUGHN:

14 Q. Such as?

15 A. There's known endogenous  
16 production of NDMA. So that's possible.  
17 It could have been an environmental  
18 exposure that led to NDMA that you found.

19 Q. What about if someone orally  
20 ingests NDMA, and after orally ingesting  
21 it, the levels of NDMA in their blood go  
22 up?

23 MS. THOMPSON: Objection to  
24 form.

1 THE WITNESS: Then that  
2 would imply to me that the dose is  
3 far exceeding the doses that we  
4 are talking about here.

5 BY MR. VAUGHN:

6 Q. Sorry. My internet is  
7 really bad here. You said that would  
8 imply to you that the dose is far  
9 exceeding the doses that we were talking  
10 about here.

11 Again, regardless of dose  
12 though, you could -- if you saw that,  
13 it's getting past the liver, correct?

14 A. Yeah. But that wouldn't be  
15 regardless of dose. It would be as a  
16 result of the dose.

17 Q. And if we saw it in the  
18 blood, that would mean that dose is  
19 sufficient to get past the liver,  
20 correct?

21 A. Correct.

22 Q. And would you also agree  
23 then once it's in the blood, there are  
24 many more organs in which the NDMA could

1 potentially impact?

2 A. There are multiple organs  
3 that receive blood flow, if that were the  
4 scenario, that would receive NDMA.

5 Q. And those tissues or organs  
6 would be at risk for cancer formation,  
7 correct?

8 A. Not necessarily.

9 Q. Why not?

10 A. Depends on the amount. It  
11 depends on that organ's ability to remove  
12 potential mutagens. And then it would  
13 also depend on that organ's volume of the  
14 specific enzyme that's involved in  
15 creating the potential mutagen from NDMA.  
16 And that specific P450 is called 2E1.  
17 I'm sorry.

18 Q. No, I'm sorry. I didn't  
19 mean to interrupt you.

20 A. It's all right.

21 And 2E1 has different  
22 amounts in different organs. So there  
23 are a lot of factors in play that would  
24 have to be considered in that

1 hypothetical.

2 Q. You used the word "mutagen."

3 What is a mutagen?

4 A. A drug that alters DNA  
5 structure.

6 Q. And is NDMA a mutagen?

7 A. Yes.

8 Q. And earlier I believe you  
9 testified that human DNA is most similar  
10 to a monkey's DNA, correct?

11 A. It most likely is. I  
12 haven't looked at that information in a  
13 long time.

14 Q. Of all the pharmaceutical  
15 medications that you've worked with, how  
16 many of them are also mutagens?

17 A. Gosh. I couldn't tell you  
18 off the top of my head. Someone would  
19 have had to have done a study  
20 specifically looking for that.

21 Most of that work is done  
22 when a drug is being developed in animal  
23 studies before preclinical development,  
24 and in most of those cases if there was

1 even a suspicion of that, it might not  
2 have continued in the drug development  
3 process. So I don't really have a good  
4 number for you.

5 Q. Why would that -- why would  
6 that be? Why, if there was a suspicion  
7 that something was a mutagen, the drug  
8 process would not continue?

9 A. Well, there's a variety of  
10 reasons that a drug would be killed in  
11 the preclinical process. In mutagenicity  
12 studies, teratogenicity studies,  
13 inability to get it stable in a dosage  
14 form, a dependency on a specific P450  
15 pathway that has a bunch of known drug  
16 interactions.

17 I mean, the list is almost  
18 endless. And the way that companies do  
19 this, is they have maybe as many as 20 or  
20 30 similar chemically related drug  
21 candidates. And they do a variety of  
22 those kind of studies on all those, and  
23 what looks like the best to go forward  
24 with are the ones that actually end up

1 making it in human trials.

2 Q. And so when a medication is  
3 found to be a mutagen, it makes more  
4 sense to kill the drug development  
5 process than potentially kill a human,  
6 right?

7 A. It depends on what the drug  
8 is being developed for.

9 Q. And in which situation do  
10 you think it would be okay to keep going  
11 and give it to a human?

12 MS. KAPKE: Object to form.

13 MS. THOMPSON: Objection to  
14 form.

15 THE WITNESS: I don't have a  
16 lot of details of that part of the  
17 drug development process.

18 So it also depends on what  
19 disease it is they're trying to  
20 treat and whether that's a risk  
21 worth taking.

22 Those are -- those are  
23 decisions made at the drug company  
24 level looking at a variety of

1 factors.

2 BY MR. VAUGHN:

3 Q. Can you name a disease for  
4 me that would be worse than cancer?

5 MS. THOMPSON: Objection.  
6 Form.

7 THE WITNESS: I mean, there  
8 are -- I don't know. There are  
9 some that I'm sure somebody can  
10 say is worse than cancer. It  
11 depends on what type of cancer  
12 we're talking about. So I don't  
13 have a strong opinion on that at  
14 all.

15 BY MR. VAUGHN:

16 Q. What type of cancer do you  
17 think is the worst kind of cancer?

18 MS. KAPKE: Object to form.

19 MS. THOMPSON: Form.

20 THE WITNESS: The fatal  
21 ones, I guess. I don't have a --

22 BY MR. VAUGHN:

23 Q. So can you name one drug  
24 that you've worked with that is a



1 mutagen?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: What do you  
5 mean by "worked with"?

6 BY MR. VAUGHN:

7 Q. Studied?

8 A. Did my own independent  
9 research on? Or as part of my 40 years  
10 of evaluating drugs and drug safety and  
11 pharmacokinetics and drug metabolism, any  
12 drug within that realm that could have  
13 turned out to be a mutagen?

14 Q. Yeah, in any way. Can you  
15 name drugs that you've worked with in  
16 some way that are mutagens?

17 A. Actos, I think, is the one  
18 that comes off the top of my head.

19 Q. What did Actos cause?

20 MS. THOMPSON: Objection.

21 Form.

22 THE WITNESS: I believe it  
23 was bladder cancer.

24 BY MR. VAUGHN:

1 Q. And was the mechanism there  
2 because it was a mutagen? Is that what  
3 was resulting in the bladder cancer?

4 A. I assume so. I didn't get  
5 into the details of the mechanisms of  
6 mutagenicity or carcinogenicity. The  
7 mechanisms of that are not what I do.

8 Q. Did you consider the  
9 mechanisms of mutagenicity when forming  
10 your opinions in this case?

11 A. Yes and no. I mean mostly  
12 what I focused on was metabolism,  
13 distribution, and drug dose-response.

14 Q. Do you know if mutagenicity  
15 has any impact on drug dose-response?

16 MS. THOMPSON: Objection.  
17 Form.

18 THE WITNESS: Well,  
19 mutagenicity would be a drug dose  
20 response, or could be.

21 BY MR. VAUGHN:

22 Q. Do you know if mutagenicity  
23 has any impact on how you should be  
24 scaling from an animal to a human?

1 MS. THOMPSON: Objection.

2 Form.

3 THE WITNESS: Well again, we  
4 have all the limitations of  
5 scaling from animals to humans.  
6 And for me to form the opinions  
7 that I did, I looked at the amount  
8 of NDMA, NDEA in valsartan  
9 products, the amounts that did not  
10 seem to be carcinogenic, in what I  
11 considered to be the best animal  
12 model which is the rat model.

13 And so my opinions were  
14 formed based on that relationship  
15 between a drug dose that did not  
16 appear to cause either -- at least  
17 carcinogenicity, and in some cases  
18 mutagenicity, and compared that to  
19 the levels of valsartan-containing  
20 products.

21 So did I consider  
22 mutagenicity as part of my  
23 evaluation? Yes, I did.

24 BY MR. VAUGHN:

1 Q. How --

2 A. In response to the drug or  
3 chemical.

4 Q. How does mutagenicity impact  
5 interspecies scaling, if at all?

6 MS. THOMPSON: Objection.

7 Form.

8 THE WITNESS: Well, I don't  
9 think -- again, it's not the  
10 mutagenicity that impacts the  
11 interspecies scaling.

12 Interspecies scaling is  
13 always going to be an  
14 extrapolation that has its  
15 limitations.

16 In every one of articles you  
17 read, in at least the last  
18 paragraph or two, it always says  
19 we're unsure what it means in  
20 humans.

21 And so we are unsure about  
22 that. And so it's hard to say how  
23 that impacts scaling because it's  
24 not -- it's an inherent problem

1 with doing the scaling to begin  
2 with.

3 BY MR. VAUGHN:

4 Q. Earlier, when we went  
5 through your CV and the literature  
6 review, you described to me the  
7 methodology in which you found that  
8 literature.

9 Did you seek out any  
10 literature on if mutagenicity would  
11 impact interspecies scaling?

12 A. I don't even know that  
13 that's the question that I was looking  
14 at.

15 What I can say is that some  
16 of the dose-response studies,  
17 particularly in rats by some of the  
18 trials, studies in rats that I relied on,  
19 they used mutagenicity as the  
20 dose-response marker.

21 Q. Did you review any  
22 literature on mutagenicity as it is  
23 related to interspecies scaling?

24 MS. THOMPSON: Objection.

1 Form.

2 THE WITNESS: Again, I'm not  
3 even sure what that question is.  
4 So I have a hard time answering  
5 it.

6 So I did say that I  
7 considered mutagenicity in making  
8 an opinion or forming an opinion  
9 about dose-response relationships  
10 with rats relative to the amount  
11 of NDMA, NDEA that are found in  
12 the valsartan products.

13 So I made those  
14 extrapolations, understanding all  
15 of the limitations quoted by  
16 almost every author in the study  
17 that I looked at.

18 BY MR. VAUGHN:

19 Q. Would you have scaled it the  
20 same way regardless of if the substance  
21 was a mutagen?

22 MS. THOMPSON: Objection.

23 Form.

24 BY MR. VAUGHN:

1 Q. Sorry, would you have scaled  
2 from the animal studies with NDMA to  
3 humans the same way regardless if the  
4 substance was a mutagen?

5 MS. THOMPSON: Objection.  
6 Form.

7 THE WITNESS: I mean, that's  
8 just one of the dose responses  
9 that you would -- that you would  
10 try and extrapolate. So I'm not  
11 even sure that I really understand  
12 the question.

13 BY MR. VAUGHN:

14 Q. Okay. If NDMA was not a  
15 mutagen, would your methodology have been  
16 the exact same?

17 A. In terms of evaluating the  
18 literature for drug distribution and  
19 metabolism, yes.

20 Q. And dose-response and  
21 interspecies scaling?

22 A. And it would have been a  
23 different response.

24 Q. I want to focus on the

1 interspecies scaling.

2 A. Okay. What do you mean by  
3 that?

4 Q. Okay. When you take it from  
5 an animal -- let's say an animal weighs  
6 one kilogram, okay?

7 A. Mm-hmm.

8 Q. And only one nanogram, let's  
9 say, for that animal can cause cancer,  
10 that 1 kg animal. How would you then --  
11 using your methodology, how would you  
12 determine how much would be needed to  
13 give a human to cause cancer?

14 MS. THOMPSON: Objection to  
15 form.

16 THE WITNESS: I didn't  
17 evaluate it in those terms that  
18 you're asking the question.

19 BY MR. VAUGHN:

20 Q. Explain to me again then how  
21 you did your analysis on these animal  
22 studies to come to these conclusions that  
23 the valsartan contained so much more NDMA  
24 than the animal studies?



1 MS. THOMPSON: Objection.

2 Form.

3 THE WITNESS: It's actually  
4 the other way around.

5 The animal study doses, that  
6 were often not related to any  
7 cancer whatsoever, so mutagenicity  
8 doesn't play a role in that  
9 setting, I was able to find doses  
10 that did not produce any mutagenic  
11 or carcinogenic effect, and those  
12 are the values that I used to make  
13 my species extrapolation from --  
14 from the rats to the humans.

15 So I was using the absence  
16 of mutagenicity and  
17 carcinogenicity, not the  
18 production of it.

19 BY MR. VAUGHN:

20 Q. Are you saying most of the  
21 animal studies regarding NDMA did not  
22 cause cancer?

23 MS. THOMPSON: Objection.

24 Form.

1 THE WITNESS: No. This gets  
2 back to my whole premise and focus  
3 in this review and report, is the  
4 dose.

5 And obviously, and we talked  
6 about this earlier this morning,  
7 you know, if you give enough NDMA  
8 and NDEA to many of the animal  
9 species that we talked about, you  
10 can induce cancer. And that's not  
11 the question that I was  
12 addressing.

13 I was addressing, is there a  
14 dose below which it doesn't appear  
15 to, and how does that relate to  
16 what's in valsartan.

17 MR. VAUGHN: Tyler, can we  
18 go back to his expert report.

19 Let's go to Page 21.

20 BY MR. VAUGHN:

21 Q. Under valsartan  
22 pharmacokinetics, can you read the first  
23 two sentences aloud for me?

24 A. "After oral administration

1 in humans, valsartan is absorbed into the  
2 body primarily in the small intestine,  
3 below the level of the stomach and  
4 reaches peak plasma concentrations  
5 between two and four hours.

6 "The amount of a given dose  
7 that reaches the systemic circulation,  
8 which means beyond the liver, is  
9 expressed by the term of absolute  
10 bioavailability and this ranges from 10  
11 to 35 percent, averaging 25 percent."

12 Q. Is there any difference  
13 between absolute bioavailability and  
14 bioavailability, the terms?

15 A. Yes, in a way. They're just  
16 adding a descriptor of absolute because  
17 they have something when they did this  
18 study to compare it to.

19 Let's say you gave a dose  
20 of -- I don't know -- any drug and you  
21 measured it in blood, then you can claim  
22 that it has bioavailability. But what  
23 you really have to do to calculate  
24 absolute bioavailability is compare that

1 back to the intravenously given dose of  
2 the same drug. And then the number that  
3 you're calculating is absolute.

4 Q. And this absolute  
5 bioavailability of valsartan is 10 to  
6 35 percent. That's in humans, right?

7 A. Correct.

8 Q. Why is the bioavailability  
9 of valsartan 350 percent higher in some  
10 humans compared to others?

11 MS. THOMPSON: Objection.  
12 Form.

13 THE WITNESS: Because of its  
14 variability, do you mean?

15 BY MR. VAUGHN:

16 Q. Well, I mean, this range of  
17 ten percent to 35 percent. 35 percent is  
18 like 350 times higher than 10 percent,  
19 right?

20 A. Yeah.

21 Q. Why is there such a wide  
22 range on the bioavailability in humans?

23 A. For many drugs you would  
24 find the same thing, so I don't consider

1 that to be abnormal at all. That's just  
2 what drug variability is.

3 Q. That's expected, right,  
4 there's going to be variability between  
5 humans?

6 A. Yes. What we call  
7 interindividual variability. But that  
8 will be unique to whatever drug we happen  
9 to be talking about.

10 Q. But typically there's  
11 variability among humans, correct,  
12 regardless of the substance?

13 A. There will always be some.  
14 In some cases it's more than this, and in  
15 some cases it's less than this in terms  
16 of the variability.

17 Q. In terms of percent  
18 bioavailability of valsartan, which  
19 animal is the most similar to humans?

20 MS. THOMPSON: Objection.  
21 Form.

22 THE WITNESS: I do not know.  
23 Because we have human data, we  
24 don't have to worry about it. And

1           so I don't know which model. I  
2           assume if I were to go back and  
3           look at the basic preclinical  
4           studies, that probably someone in  
5           Novartis or contracted by Novartis  
6           did 25 to 30 years ago, that I  
7           could probably find that. But --  
8           and so I know it's out there. I  
9           just haven't looked at it.

10       BY MR. VAUGHN:

11           Q.       Do you agree that knowing a  
12       medication's bioavailability is critical  
13       in determining the dose necessary for a  
14       specific outcome?

15                   MS. THOMPSON: Objection to  
16       form.

17                   THE WITNESS: Well, the way  
18       that question is asked, you know,  
19       could go a lot of different  
20       answers.

21                   You know, if only 5 percent  
22       of something is absorbed, but you  
23       give a high enough dose to get the  
24       effect, then it's the effect you

1           care about, and not whether it was  
2           5 percent and whether you liked  
3           the number 5 percent or not.

4   BY MR. VAUGHN:

5           Q.     This 10 to 35 percent  
6           bioavailability in your report, that's  
7           specific to valsartan, right? That  
8           doesn't have anything to do with the  
9           bioavailability of NDMA or NDEA, correct?

10          A.     Nothing to do with that at  
11          all. They -- they're not attached to  
12          each other. One doesn't carry the other.  
13          So they're managed and handled  
14          independently.

15          Q.     Can you identify in your  
16          report where you specified the  
17          bioavailability of NDMA in humans?

18          A.     I think in my report -- if  
19          you give me a minute to look at it. Is  
20          that all right?

21          Q.     Absolutely. Take all the  
22          time you need.

23          A.     You're talking about NDMA or  
24          NDEA?

1 Q. Yes, sir.

2 A. Yeah, I don't find where I  
3 specifically listed a specific  
4 bioavailability number. And the reason  
5 probably for that is that it depends on  
6 the dose because, unlike valsartan, this  
7 is a highly subjective drug to first-pass  
8 metabolism. And so as the dose goes up,  
9 the bioavailability changes.

10 So it's not as fixed a  
11 number as the valsartan bioavailability  
12 would be.

13 Q. If there were studies in  
14 which they were giving below -- scratch  
15 that.

16 If there were studies in  
17 which they were giving NDMA below what  
18 would saturate the liver, would that  
19 allow you to determine its  
20 bioavailability?

21 A. Well, actually what you  
22 would determine in that setting by  
23 measuring something downstream from the  
24 liver, you would measure zero, which



1 would mean it was essentially zero  
2 bioavailability because it wouldn't get  
3 into the systemic circulation, despite  
4 being absorbed.

5 Q. So it's your opinion the  
6 liver must be fully saturated before it  
7 can get past the liver?

8 A. Absolutely.

9 Q. Is that with every animal?

10 A. That's with everybody with a  
11 liver.

12 Q. And then -- so once it's  
13 saturated, is every amount of the dose  
14 going to be going past the liver?

15 A. Yes. Depends again on the  
16 compound, the drug, and how else it might  
17 be metabolized. But when it leaves the  
18 liver, it goes into the venous  
19 circulation.

20 Q. And so can you explain to me  
21 again how you determine the  
22 bioavailability of a substance?

23 A. The most pure way, if you  
24 will -- excuse me -- is to give an oral

1 dose and an IV dose and compare how much  
2 you measure in the bloodstream using  
3 something called the area under the curve  
4 or the AUC.

5 Q. And did you see any studies  
6 like that on any animal?

7 A. I did.

8 Q. What animals?

9 A. Predominately rats. But a  
10 few other species. I think I saw a  
11 monkey study and a pig study and a dog  
12 study. Actually two dog studies, maybe.

13 Q. And do you recall what the  
14 bioavailability of NDMA is in rats?

15 A. It was less than 10 percent  
16 at doses below, say, around .1 milligram  
17 per kilogram given orally. So in the  
18 range of 6 to 8 percent.

19 Q. What about monkey? Do you  
20 recall what the bioavailability of NDMA  
21 is in a monkey?

22 A. I think the study I saw was  
23 it was higher. Maybe as much as 80 or  
24 90 percent.

1 Q. 80 or 90 percent?

2 A. That's my recollection.

3 Q. So you're saying in monkeys,  
4 80 to 90 percent of the NDMA you give  
5 them is going to get past the liver?

6 MS. THOMPSON: Objection.

7 Form.

8 THE WITNESS: In the dose  
9 that they gave in that monkey  
10 study. That's going to get  
11 back -- gets back to the heart of  
12 what my whole premise here is, is  
13 that bioavailability for a  
14 high-clearance drug like NDMA is  
15 based on the dose you give.

16 And I'm fairly certain in  
17 the monkey study that it gave at  
18 least a milligram per kilogram,  
19 which is way above what I'm  
20 contending is the liver's capacity  
21 to completely metabolize NDMA and  
22 spare downstream organs.

23 BY MR. VAUGHN:

24 Q. What about pigs? Do you

1 recall the bioavailability of NDMA in  
2 pigs?

3 A. Yeah. I think that study  
4 was around -- oh, I'm going to say  
5 45 percent, something like that.

6 Q. And then do you recall the  
7 bioavailability of NDMA in dogs?

8 A. I think it was somewhat  
9 similar to the pigs. Maybe in that 40 to  
10 50, 60 percent range.

11 Q. And so pigs, dogs, monkeys,  
12 the bioavailability of NDMA is hundreds  
13 of times higher than in rats, correct?

14 A. When you give a thousand  
15 times higher dose, yes.

16 Q. But it's your opinion that  
17 humans are most similar to rats in their  
18 bioavailability of NDMA?

19 A. That is my contention. And  
20 there's literature to support that.

21 Q. Is there literature that  
22 goes against that?

23 MS. THOMPSON: Objection.

24 Form.

1 THE WITNESS: Again, you  
2 have to be very specific about the  
3 doses given.

4 And the other animal species  
5 that you're talking about, the  
6 doses given were a thousand or  
7 more times higher than the doses  
8 that I'm talking about in the rat  
9 studies that have been shown to be  
10 completely metabolized in the  
11 liver.

12 MR. VAUGHN: Give me just  
13 one second.

14 THE WITNESS: And I should  
15 add, while you're looking,  
16 there's -- it's a little more  
17 complicated than that.

18 When you look at these kinds  
19 of bioavailability studies, not  
20 only is the dose important to  
21 determine what you're going to  
22 call bioavailability, the two  
23 other things that are important to  
24 look at, one is interspecies

1 differences in the amount of the  
2 cytochrome P450 enzyme that we're  
3 talking about here, which is 2E1.

4 And so for a species to have  
5 less than a rat, let's say, then  
6 even the same dose would give a  
7 higher bioavailability because  
8 they have less metabolizing  
9 capacity by having less 2E1. And  
10 beagles, swine, and monkey  
11 primates are all known to have  
12 less 2E1 than rats.

13 So that factors into that  
14 higher bioavailability.

15 And then to go even a little  
16 bit deeper, and this gets into the  
17 understanding of how you calculate  
18 or use AUCs to calculate  
19 bioavailability, is there's an  
20 assumption that you make. And all  
21 of these articles we're referring  
22 to identify that assumption.

23 And they clearly identify in  
24 their own self-criticism of their

1 study, is it makes the assumption  
2 that when you give a drug IV, it's  
3 metabolized nowhere but in the  
4 liver because you're comparing the  
5 oral dose that goes straight  
6 through the liver with the IV  
7 dose.

8 And the more there is  
9 extrahepatic metabolism of the  
10 drug, the more the overestimate is  
11 of the bioavailability.

12 So using those  
13 bioavailability numbers in animals  
14 that have less 2E1 that made  
15 invalid assumptions about the  
16 calculations of bioavailability to  
17 begin with, and then thirdly give  
18 a thousandfold or higher dose than  
19 what the liver can handle at  
20 smaller doses, then I evaluated  
21 those studies, but because I  
22 didn't think they were germane to  
23 the doses of NDMA that we're  
24 talking about here, they didn't

1           alter my opinions in my report.

2       BY MR. VAUGHN:

3           Q.       Part of the reasons those  
4       doses were not -- or you do not consider  
5       similar to the amounts given to humans is  
6       because humans weigh more than those  
7       animals, correct?

8           A.       No. You can do it on a  
9       milligram per kilogram.

10                   The three other species  
11       studies we're talking about, beagles,  
12       pig, and monkey, some of them gave both 1  
13       and 5-milligram-per-kilogram oral doses.  
14       And if you do that on a scale of what's  
15       in valsartan containing NDMA, we are  
16       talking thousands and thousands times  
17       higher doses.

18                   And I think it might have  
19       been the monkey study that only gave one  
20       milligram per kilogram. They didn't do  
21       the five as well.

22                   So there are a lot -- there  
23       are a lot of reasons why those trials did  
24       not alter my conclusions, because they



1 weren't relevant to the doses that we are  
2 talking about, and they weren't as close  
3 a species for 2E1 metabolism.

4 Q. And you're saying humans are  
5 more similar to rats than monkeys?

6 MS. THOMPSON: Objection to  
7 form.

8 THE WITNESS: In 2E1  
9 metabolism.

10 BY MR. VAUGHN:

11 Q. Doctor, we got through that  
12 section a little quicker than I had  
13 anticipated.

14 MR. VAUGHN: I think it's a  
15 little after noon your guys' time.  
16 If you want to take a lunch break  
17 now, I think that would be --  
18 that's okay with me.

19 MS. THOMPSON: That's fine  
20 with me.

21 THE WITNESS: Yeah, that's  
22 fine.

23 MR. VAUGHN: How long do you  
24 guys want to take? We can go off

1 the record.

2 THE VIDEOGRAPHER: The time  
3 now is 12:16 p.m. We're off the  
4 record.

5 (Whereupon a luncheon recess  
6 was taken.)

7 THE VIDEOGRAPHER: The time  
8 right now is 1:07 p.m. We're back  
9 on the record.

10 BY MR. VAUGHN:

11 Q. Doctor, you testified  
12 earlier that NDMA is a probable human  
13 carcinogen. Can you define for the jury  
14 the word "probable"?

15 A. Again, I take that  
16 definition from the IARC definition of a  
17 known carcinogen in animals, but  
18 insufficient data to call it a known  
19 carcinogen in humans.

20 Q. Do you not have a definition  
21 for the word "probable"?

22 MS. THOMPSON: Objection.  
23 Form.

24 THE WITNESS: No, I don't.

1 BY MR. VAUGHN:

2 Q. Would you say that probable  
3 is the same as more likely than not or a  
4 higher level of proof?

5 MS. THOMPSON: Objection to  
6 form.

7 THE WITNESS: Yeah, I don't  
8 have an opinion on that.

9 BY MR. VAUGHN:

10 Q. Do you think probable is  
11 possibly less than more likely than not?

12 MS. THOMPSON: Objection to  
13 form.

14 THE WITNESS: I don't have  
15 an opinion on that.

16 BY MR. VAUGHN:

17 Q. Does the bioavailability of  
18 valsartan decrease as you decrease the  
19 dose of valsartan?

20 MS. THOMPSON: Objection.  
21 Form.

22 THE WITNESS: Not that I'm  
23 aware of.

24 I don't recall seeing

1 anything in the -- in the  
2 pharmacokinetic valsartan studies  
3 that indicated that. So it's  
4 probably of a similar amount  
5 across its usual oral dosage  
6 range.

7 BY MR. VAUGHN:

8 Q. Is that typical of most  
9 drugs?

10 A. It depends. It depends on  
11 their clearance and how they're  
12 metabolized and what their dose range is.

13 Q. So why would valsartan --  
14 because do you have to saturate it  
15 before -- beforehand, the liver, before  
16 it can get systemic?

17 MS. THOMPSON: Objection.  
18 Form.

19 THE WITNESS: Well, unless  
20 you're giving a drug orally with  
21 the intent of treating the colon,  
22 which is like what happens with  
23 some drugs for ulcerative colitis  
24 and Crohn's disease, then orally

1           administered drugs that are  
2           supposed to have an effect  
3           somewhere other than the colon or  
4           the liver, then you have to give  
5           it at a dose that will get to  
6           those sites of action.

7                       But I wouldn't characterize  
8           the metabolism as having been  
9           saturated at the doses that we  
10          give for valsartan.

11 BY MR. VAUGHN:

12           Q.       If valsartan is not  
13          saturated in the liver then why is some  
14          of the valsartan getting past the liver?

15                    MS. THOMPSON: Objection.  
16          Form.

17                    THE WITNESS: In this case  
18          it's a slowly metabolized drug.  
19          So it just takes a while to  
20          metabolize. So some drug is going  
21          on into the bloodstream while the  
22          other part that's still in the  
23          liver is waiting to be  
24          metabolized.

1                   So, I mean, you could call  
2                   that a form of saturation if you  
3                   want. But it's -- it's not really  
4                   a form of saturation. It's a rate  
5                   of metabolism in this case.

6 BY MR. VAUGHN:

7                   Q. And so I'm clear, the  
8                   valsartan does not have to saturate the  
9                   liver to get past the liver, correct?

10                  MS. THOMPSON: Objection.  
11                  Form.

12                  THE WITNESS: I don't  
13                  believe I've ever seen that  
14                  described as being a saturable  
15                  metabolism step.

16 BY MR. VAUGHN:

17                  Q. Why with NDMA do you believe  
18                  that it must fully saturate the liver for  
19                  any amount of NDMA to get past the liver?

20                  MS. THOMPSON: Objection.  
21                  Form.

22                  THE WITNESS: Because its  
23                  rate of metabolism is different.  
24                  It's a faster rate.

1 BY MR. VAUGHN:

2 Q. What's the rate of  
3 metabolism of NDMA?

4 A. I don't know that number off  
5 the top of my head.

6 Q. What's the rate of  
7 metabolism for valsartan?

8 A. I also don't know the number  
9 off the top of my hand -- my head.

10 My point is that using the  
11 term "saturation" to define what does or  
12 does not get into the liver past the  
13 bloodstream, it's more complicated than  
14 that. It's based on rate of metabolism  
15 and the amount given as well.

16 Q. How can you have the opinion  
17 that NDMA is metabolized faster than  
18 valsartan when you do not know the rate  
19 of metabolism of either valsartan or  
20 NDMA?

21 MS. THOMPSON: Objection.  
22 Form.

23 THE WITNESS: Just its  
24 clearance. Clearance.

1 BY MR. VAUGHN:

2 Q. Can you explain that a  
3 little more?

4 A. Well, there's two types of  
5 clearance. There's high clearance and  
6 low clearance. And it depends on the  
7 kind of drug and which one is going to be  
8 more dependent on the intrinsic clearance  
9 of the liver versus hepatic blood flow  
10 itself.

11 And those ratios are all  
12 different for different drugs.

13 Q. Are you aware of any  
14 substances that can inhibit P450?

15 A. Yes. I'm aware of many.

16 Q. Can you list off the ones  
17 that you're aware of?

18 A. Amiodarone, cimetidine,  
19 azole antifungals, erythromycin,  
20 clarithromycin, many of the HIV drugs.  
21 The list goes on and on.

22 Q. So taking substances that  
23 inhibit P450 increase the likelihood that  
24 NDMA is going to get past the liver in a



1 human?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: Again, it  
5 would depend on what the inhibitor  
6 inhibits.

7 Some of these drugs I  
8 mentioned only block P450-3A4 and  
9 they don't touch 2E1, which is the  
10 major P450 we're talking about  
11 here. And in looking at my 2E1  
12 metabolism, there are no listed  
13 inhibitors for 2E1.

14 BY MR. VAUGHN:

15 Q. None?

16 A. None.

17 Q. What about alcohol?

18 A. Alcohol. You asked me about  
19 drugs. And so I didn't list alcohol as a  
20 drug.

21 Q. I apologize. So alcohol  
22 could though?

23 A. Alcohol has been shown to  
24 block 2E1.

1 Q. So it would be a bad idea to  
2 be drinking alcohol if you were taking  
3 valsartan contaminated with NDMA,  
4 correct?

5 A. Actually, I should --

6 MS. THOMPSON: Objection to  
7 form.

8 THE WITNESS: Sorry.

9 Let me clarify. I think  
10 it's the alcohol that blocks 2A6  
11 and not 2E1.

12 BY MR. VAUGHN:

13 Q. And what are you basing that  
14 on?

15 A. The data.

16 Q. Are you aware of any other  
17 substances -- doesn't have to be drugs --  
18 any other substances that would inhibit  
19 2E1?

20 A. I am not.

21 Q. What data are you relying on  
22 to say that alcohol does not inhibit 2E1?

23 A. The fact that there isn't  
24 any.

1 Q. So you're not aware of any?

2 A. I'm not aware of any.

3 Q. So you did not -- sorry.

4 A. I'm aware though of the  
5 alcohol and the 2A6.

6 Q. If there is literature out  
7 there on various substances that can  
8 inhibit 2E1, you did not consider those  
9 in forming your opinions in this case,  
10 correct?

11 MS. THOMPSON: Objection.

12 THE WITNESS: I did not see  
13 any.

14 Sorry.

15 MS. THOMPSON: You got to  
16 let me object.

17 Objection to form.

18 Go ahead.

19 THE WITNESS: I did not see  
20 any.

21 BY MR. VAUGHN:

22 Q. And so, therefore, you did  
23 not consider it, correct?

24 A. Correct.

1 Q. Doctor, do you disagree with  
2 the plaintiffs' experts that there is a  
3 linear dose-response with NDMA or NDEA  
4 and cancer with no dose threshold,  
5 correct?

6 MS. KAPKE: Object to form.

7 MR. VAUGHN: Let me re-ask  
8 that one.

9 BY MR. VAUGHN:

10 Q. Doctor, are you aware if  
11 sedatives can impact 2E1 or inhibit 2E1?

12 MS. THOMPSON: Object to  
13 form.

14 THE WITNESS: I don't recall  
15 specifically seeing that. If I  
16 did, my recollection was that it  
17 was one of the older sedatives  
18 that we don't use anymore. But  
19 I -- I don't have that off the top  
20 of my head.

21 BY MR. VAUGHN:

22 Q. So you do think that there  
23 are some substances that can inhibit 2E1?

24 A. Maybe.

1 Q. Maybe. What about  
2 phytochemicals?

3 A. I'm not sure what you're  
4 referring to.

5 Q. Chemical compounds produced  
6 by plants. Are you aware of any  
7 compounds that plants could produce that  
8 could inhibit 2E1?

9 A. If there is, I didn't look  
10 at that or I didn't consider it.

11 Q. Okay. Doctor, plaintiffs'  
12 experts have opined that NDMA and cancer  
13 have a linear dose-response with no dose  
14 threshold. You disagree with that  
15 opinion, correct?

16 MS. KAPKE: Object to form.

17 THE WITNESS: I disagree  
18 with the latter part of that  
19 conclusion about no dose  
20 threshold, because that's not  
21 consistent with the data that I've  
22 included in my report.

23 BY MR. VAUGHN:

24 Q. Okay. Have you seen any

1 evidence or literature suggesting that  
2 there is a no-dose threshold?

3 A. Yes. I refer in my  
4 report -- excuse me. The Ito study.

5 Q. You said Ito?

6 A. I-T-O.

7 Q. Okay. Ito. Gotcha.

8 A. There was a noneffective  
9 level of carcinogenesis at .1 milligrams  
10 per kilogram by the oral route.

11 Q. Is that the only thing that  
12 you're basing your opinion off of?

13 A. No.

14 Q. What else?

15 A. One of the Peto studies on  
16 Page 34. The apparent increase in liver  
17 cancer was only seen in doses above  
18 .3 parts per million, equating to  
19 15 micrograms per kilogram per day.

20 Q. So you actually relied on  
21 Peto to say there is no dose-response --  
22 or there is no -- I'm sorry, there is no  
23 dose threshold?

24 MS. THOMPSON: Objection to

1 form.

2 THE WITNESS: I'm relying on  
3 that particular Peto study. And  
4 this is in -- this is in comparing  
5 against his rate of nontreated  
6 rats who also developed liver  
7 cancer.

8 So evidence of higher doses,  
9 yes, but not at the dose different  
10 from what was seen in the  
11 background noise of his rat  
12 population.

13 BY MR. VAUGHN:

14 Q. Do you know if Peto believes  
15 there is a no-dose threshold?

16 A. I may --

17 MS. THOMPSON: Object to the  
18 form. Sorry.

19 THE WITNESS: Yeah, I may  
20 have mentioned it in my report  
21 that he uses terms about the  
22 likely shapes of dose-response.  
23 And that's on Page 36 in my  
24 report.

1 "In Peto's conclusion is the  
2 comment, 'General arguments about  
3 the likely shapes of dose-response  
4 relationships make it probable,  
5 even at lower doses where direct  
6 observation is impractical, that  
7 this linear relationship may  
8 remain approximately true for  
9 Colworth rats, if not for  
10 humans.' "

11 And so he's not sure at the  
12 low doses if there's enough  
13 evidence to solidly state that  
14 there is a linear relationship.

15 BY MR. VAUGHN:

16 Q. He's not 100 percent sure,  
17 but he thinks it's probable, correct?

18 A. He think it's possible,  
19 probable. I'm just saying that the  
20 people who do those studies are not  
21 100 percent convinced at the low doses.

22 Q. They are not 100 percent.  
23 But they think it's probable, correct?

24 MS. THOMPSON: Objection to



1 form.

2 THE WITNESS: That's not the  
3 word he used. He said  
4 "approximately true." So he  
5 didn't use the word "probable."  
6 That was your word.

7 BY MR. VAUGHN:

8 Q. Approximately true. Oh.  
9 Would you at least think that's more  
10 likely than not?

11 A. I do not know what he meant  
12 by that.

13 Q. Okay.

14 A. And what it does mean is  
15 that he can draw through the numbers and  
16 call it a straight line, but that doesn't  
17 mean that it actually describes what  
18 happens at low doses like we're talking  
19 about because he didn't do enough animals  
20 and you don't see enough cancer at those  
21 doses to have reliability.

22 And one of his areas of  
23 statistical analysis in that study  
24 involved something called his Z value.

1                   And I go onto describe on  
2   the next page, in his methodology, the Z  
3   value, if it's between -- between the  
4   numbers two and three, then judgment as  
5   to how likely it is that treatment really  
6   did cause the disease of interest becomes  
7   more difficult.

8                   And so he's unclear as well,  
9   because in the ones that we are talking  
10   about at these doses we're talking about  
11   were in that range of uncertainty with  
12   that Z value between two and three.

13               Q.     Again, when you say he's not  
14   sure, do you mean that, you know, he's --  
15   what was the word you used, approximately  
16   true?

17               A.     That was his previous  
18   statement.

19               Q.     So you rely on Peto to say  
20   that there is a threshold, but you  
21   disagree with Peto's analysis of his own  
22   studies?

23               A.     I do not -- sorry.

24                   MS. THOMPSON:   Objection to

1 form.

2 THE WITNESS: I do not  
3 disagree. That's not what I said.  
4 I said he is unsure at those  
5 low doses. And I am agreeing with  
6 him at those low doses about the  
7 uncertainty of a linear  
8 relationship at doses that low.

9 BY MR. VAUGHN:

10 Q. Do you agree with him that  
11 it's approximately true?

12 A. I agree that he can draw a  
13 line through them and then claim that's  
14 approximately true.

15 And I would just like to add  
16 that this is an era at the time where  
17 everyone pretty much already believed  
18 that it was linear. And so to me, he was  
19 trying to not accept that it might not  
20 be.

21 And I think there are other  
22 experts in this field who might argue  
23 that we have more modern data that  
24 dispute a low range linearity

1 relationship.

2 Q. Approximately what year was  
3 Peto's study going on?

4 A. 1991 for this one. So  
5 30 years ago.

6 Q. If you didn't know what Peto  
7 meant by approximately true, wouldn't you  
8 want to see what he meant by that  
9 wording?

10 MS. THOMPSON: Objection.  
11 Form.

12 THE WITNESS: I think if he  
13 was able to give more detail on  
14 what he meant, he would have put  
15 it in his paper. So I'm only  
16 going on what he put on his paper.

17 BY MR. VAUGHN:

18 Q. Have you not reviewed any of  
19 Peto's other papers where he says that  
20 there's likely no threshold for NDMA?

21 A. I have read his other  
22 papers.

23 Q. And do you recall him saying  
24 that it is likely there is no threshold

1 for NDMA?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: I recall him  
5 saying that. But that's not what  
6 this study data shows.

7 BY MR. VAUGHN:

8 Q. And so are you disagreeing  
9 with Peto that it is likely there is no  
10 threshold for NDMA?

11 MS. THOMPSON: Objection.  
12 Form.

13 THE WITNESS: Again, I'm  
14 disagreeing that the data show  
15 that. We're talking now about his  
16 interpretation of his data at an  
17 era where linearity was the  
18 accepted, and which we now know is  
19 not necessarily the case.

20 BY MR. VAUGHN:

21 Q. Can you explain to the jury  
22 what a linear dose-response means?

23 A. In this case it means that  
24 you can identify with dose increases

1 across a broad enough dose range that you  
2 see an increase in the effect. And that  
3 effect could be a positive effect or it  
4 could be a negative effect.

5 And I think all of the  
6 papers in this realm that talk about low  
7 doses, that the effect rates are so small  
8 that you start losing your reliability of  
9 that linear relationship.

10 The Brantom study, which is  
11 the next one at the bottom of Page 37, in  
12 Brantom's introductory remarks he  
13 considers the possibility that at very  
14 low levels of exposure there is no  
15 effect.

16 And he did essentially a  
17 similar study to what Peto did.

18 Q. He considers the  
19 possibility. Is that what you said?

20 A. That's a quote in my -- in  
21 my report from what he says in the  
22 introductory components to his thesis  
23 project.

24 Q. So he thinks there's some

1 possibility that there might not be a  
2 threshold?

3 MS. THOMPSON: Objection.  
4 Form.

5 THE WITNESS: That's what he  
6 says.

7 BY MR. VAUGHN:

8 Q. But you're convinced there  
9 is a threshold?

10 MS. THOMPSON: Objection.  
11 Form.

12 THE WITNESS: I believe  
13 there is a threshold, yes.

14 BY MR. VAUGHN:

15 Q. And so is it your opinion  
16 that you can consume a certain amount of  
17 NDMA per day and not be at any increased  
18 risk of developing cancer, but once you  
19 pass some threshold, then boom, you can  
20 start developing cancer?

21 MS. THOMPSON: Objection.  
22 Form.

23 THE WITNESS: That would  
24 mischaracterize what I've written

1 in my report.

2 BY MR. VAUGHN:

3 Q. How did I mischaracterize  
4 it?

5 A. I have identified a level  
6 below which, number one, there does not  
7 appear to be proof of a cancer effect,  
8 again, in rat studies. And that I  
9 further go on to say that's consistent  
10 with first-pass metabolism at low doses  
11 of this kind of compound, and that these  
12 reported no cancer rates are hundreds to  
13 thousands of times higher than the amount  
14 of NDMA found in any of the valsartan  
15 products.

16 Q. Based on your methodology,  
17 correct?

18 A. Based on what's in the  
19 literature.

20 Q. Okay. But, I mean, the dose  
21 comparison, you're the one that did that  
22 calculation, right?

23 A. I did. But I didn't create  
24 the noncancer dose that I'm reporting



1 from these studies like Ito.

2 Q. But to take the animal dose  
3 to get the human dose, you're the one  
4 that did that math, right?

5 A. Yes.

6 Q. All right. And we'll get to  
7 your methodology on that later.

8 In your opinion, what is the  
9 threshold level of NDMA that is needed to  
10 increase a human's risk of getting  
11 cancer?

12 MS. THOMPSON: Objection.  
13 Form. Asked and answered.

14 THE WITNESS: I do not know  
15 that dose. As I've said  
16 previously, I'm able to identify  
17 what appears to be a dose below  
18 which you don't see cancer. I  
19 don't have the ability to identify  
20 above which, because at these low  
21 dose exposure levels that seem  
22 they don't cause cancer or that do  
23 not cause cancer in animal  
24 studies, often the next dose is

1 100 or a thousand times.

2 So there may be something in  
3 between. I don't know where that  
4 is.

5 So I'm only talking about  
6 the no effect dose. I'm not  
7 trying to describe or define the  
8 effect dose.

9 BY MR. VAUGHN:

10 Q. Is this mysterious threshold  
11 for NDMA in humans, is it the exact same  
12 for every person?

13 MS. THOMPSON: Objection.  
14 Form.

15 THE WITNESS: Since I don't  
16 know what it is, I can't answer  
17 that.

18 BY MR. VAUGHN:

19 Q. Is it your opinion that once  
20 that threshold is crossed, the  
21 dose-response then would be linear from  
22 then on?

23 MS. THOMPSON: Objection.  
24 Form.

1 THE WITNESS: That's not  
2 what I said.

3 What I said is the amount of  
4 NDMA in any valsartan product is  
5 hundreds to thousand times below  
6 doses that are no cancer related  
7 in the rat studies.

8 BY MR. VAUGHN:

9 Q. I'm sorry. I wasn't clear  
10 in my question probably.

11 Valsartan aside. If you're  
12 giving a human NDMA, once you pass  
13 whatever that threshold is, is the  
14 dose-response going to be linear?

15 A. We don't know that in  
16 humans. I have no idea. There's never  
17 been a --

18 Q. Is there a chance that it  
19 becomes exponential at some point, it  
20 kind of goes straight up?

21 A. I have no idea.

22 MS. THOMPSON: Objection.

23 BY MR. VAUGHN:

24 Q. What -- how do you define

1 whether you have a linear dose-response?  
2 What does the word "linear" in the  
3 dose-response mean?

4 A. It depends on what the  
5 response is.

6 Q. Can you explain that to me,  
7 what you mean?

8 A. Well, which response are we  
9 talking about?

10 Q. Well, let's talk about NDMA  
11 and its ability to increase the risk of  
12 cancer. So what is a linear  
13 dose-response mean in that context?

14 A. In that context it's defined  
15 a couple of different ways.

16 Pegg defined it by looking  
17 at the formation of adducts.

18 Peto defined it by the  
19 formation of tumors so there are  
20 different ways of defining that.

21 Q. But the linear part of it,  
22 what does that mean? Does that mean,  
23 like, it's proportional to the amount  
24 that you increase the dose to increase

1 risk of cancer? Is that what's going on  
2 with linear?

3 A. Again, the use of the term  
4 linear means as the dose goes up, it  
5 looks like the occurrence goes up, which  
6 may or may not necessarily be  
7 characterized as a dead straight line.  
8 They just sort of observe that there's  
9 more when they sort of plot it over time.

10 Q. Is there a reason that  
11 throughout your entire expert report you  
12 never mention that NDMA is genotoxic?

13 MS. THOMPSON: Objection.  
14 Form.

15 THE WITNESS: There's no  
16 reason that I didn't mention it.  
17 It was not what I was focused on  
18 in my report.

19 BY MR. VAUGHN:

20 Q. Do you know if NDMA is  
21 genotoxin?

22 MS. THOMPSON: Objection.  
23 Form.

24 THE WITNESS: We know it is

1 in animals.

2 BY MR. VAUGHN:

3 Q. Do you know if a substance  
4 being a genotoxin impacts its dose  
5 threshold?

6 MS. THOMPSON: Objection.

7 Form.

8 THE WITNESS: I don't even  
9 understand the question. So I'm  
10 not sure how to answer it.

11 BY MR. VAUGHN:

12 Q. Okay. So you didn't  
13 consider the fact that NDMA is a  
14 genotoxin when coming to your opinions  
15 that there is a threshold for NDMA  
16 exposure before it's going to increase  
17 the risk of cancer, correct?

18 A. Well, not correct, because  
19 that's not what I testified.

20 I'm not defining, again, the  
21 threshold at which genotoxicity occurs.  
22 That wasn't the focus of my report.

23 Q. There's -- I think you kind  
24 of misconstrued things. I don't think

1 there's a threshold for genotoxicity.

2 NDMA is just a genotoxin, period,

3 correct?

4 A. Yes, it's a genotoxin.

5 Q. At any amount given, right?

6 A. Well, I don't know about  
7 that. That sort of gets out of my area  
8 of testimony, because there are  
9 oncologists and toxicologists that that's  
10 more within their realm.

11 I'm more looking at more  
12 dose-response relationships at what  
13 appear to be safe levels of NDMA and how  
14 that compares to the amount of NDMA found  
15 in valsartan products.

16 Q. And so you would defer to an  
17 oncologist or a toxicologist on if the  
18 genotoxicity of a substance would impact  
19 it's dose threshold?

20 MS. THOMPSON: Objection.

21 THE WITNESS: Not

22 necessarily, but again, I don't  
23 know that I understand what that  
24 question was asking.

1 BY MR. VAUGHN:

2 Q. Do you know or have you seen  
3 any literature that says that you should  
4 calculate the dose-response or the  
5 threshold differently if the substance is  
6 a genotoxin?

7 MS. THOMPSON: Objection.  
8 Form.

9 THE WITNESS: Characterizing  
10 dose-response relationships has  
11 nothing to do with whether a  
12 chemical or a drug is genotoxic or  
13 not.

14 BY MR. VAUGHN:

15 Q. What about dose threshold?

16 A. Again, depends on the  
17 response. But there are many drugs where  
18 you calculate a dose threshold that has  
19 nothing to do with genotoxicity.

20 Q. There are many drugs that  
21 you can calculate -- sorry, scratch that.

22 Can you name one genotoxin  
23 that has a threshold level needed to --  
24 scratch that again. I'm sorry.



1 Can you name one genotoxin  
2 that has a dose threshold?

3 MS. THOMPSON: Objection.  
4 Form.

5 THE WITNESS: A dose  
6 threshold for what?

7 BY MR. VAUGHN:

8 Q. Before it can cause cancer.

9 A. No. I mean, that's what I  
10 previously testified is that I'm not here  
11 today to try to define the genotoxic dose  
12 threshold that starts causing  
13 genotoxicity. That's not the nature of  
14 my report.

15 Q. Then how can you say that  
16 there is a dose threshold for NDMA?

17 A. And I'll say again, it's the  
18 dose from the studies that was shown to  
19 not be genotoxic.

20 Q. And so that's all that you  
21 base your opinion on, correct?

22 A. That is what I'm basing my  
23 opinion on.

24 Q. Thank you. Can you define

1 genotoxic to the jury for me?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: I don't think  
5 that's my role to do that.

6 Again, I'm focusing on drug  
7 metabolism. I think there are  
8 others who have spent time on  
9 toxicity, genotoxicity,  
10 mutagenicity. They're better  
11 equipped to do that than I am. So  
12 it's not my role.

13 BY MR. VAUGHN:

14 Q. And you would defer to them,  
15 correct?

16 A. In the definition of  
17 genotoxicity, yes, I would.

18 Q. And that's the only aspect  
19 that you would defer to them on, is just  
20 the definition?

21 MS. THOMPSON: Objection.

22 Form.

23 THE WITNESS: I never said  
24 it was the only aspect I would

1           refer to them on. I said that  
2           specific question is one that I  
3           think it's -- I would defer to  
4           them.

5 BY MR. VAUGHN:

6           Q.       Do you know if a genotoxin  
7           can permanently alter a person's DNA?

8                   MS. THOMPSON: Objection.  
9           Form.

10                  THE WITNESS: I have no  
11           opinion on that.

12 BY MR. VAUGHN:

13           Q.       So you have no definition of  
14           genotoxicity?

15                  MS. THOMPSON: Objection.  
16           Form.

17                  THE WITNESS: I do not.

18 BY MR. VAUGHN:

19           Q.       And I assume you probably  
20           have no opinion if it does permanently  
21           mutate someone's DNA, if that can be  
22           passed to every generation thereafter?

23                  MS. THOMPSON: Objection.  
24           Form.

1 THE WITNESS: I do not have  
2 an opinion on that.

3 BY MR. VAUGHN:

4 Q. Let's go to Page 26 of your  
5 expert report. The first paragraph at  
6 the bottom, if you can read us the first  
7 sentence that starts with, "The alpha."

8 A. "The alpha-hydroxylation  
9 pathway produces the methyldiazonium ion,  
10 which binds with a segment of DNA to  
11 produce a primary mutagenic and  
12 carcinogenic substance  
13 O6-methyl-guanine."

14 Q. Can you explain what that  
15 means to the jury?

16 A. Well, to me, what it means  
17 particularly if you put it in the context  
18 of the following sentence, is that the  
19 key step in producing the potential  
20 mutagenic carcinogenic substance is  
21 forming the alpha-hydroxylated metabolite  
22 of NDMA, which is 2E1-mediated.

23 Q. Is it okay if we refer to  
24 this as O6 going forward?

1 A. Sure.

2 Q. It's a lot to say. Thank  
3 you. And so you would agree that O6 is a  
4 carcinogen, correct?

5 MS. THOMPSON: Objection.  
6 Form.

7 THE WITNESS: That is the  
8 known carcinogen, correct.

9 BY MR. VAUGHN:

10 Q. And so O6 is not a probable  
11 human carcinogen. O6 is a known human  
12 carcinogen, correct?

13 MS. THOMPSON: Objection to  
14 form.

15 THE WITNESS: Incorrect. We  
16 do not know the known carcinogenic  
17 effect of NDMA or its downstream  
18 metabolites.

19 BY MR. VAUGHN:

20 Q. Why did -- in your report,  
21 do you note that O6 is a carcinogenic  
22 substance?

23 A. Because it caused cancer in  
24 animals.

1 Q. Oh, so you're talking about  
2 animals. You are not talking about  
3 humans?

4 A. Yes.

5 Q. You think O6 is unlikely to  
6 cause cancer in humans?

7 MS. THOMPSON: Objection.  
8 Form.

9 THE WITNESS: I never said  
10 that. I think that's, again, a  
11 better question for toxicology  
12 oncology. The amounts, the  
13 mechanism, the inherent protective  
14 mechanisms. That's not the nature  
15 of my testimony.

16 BY MR. VAUGHN:

17 Q. The amount, you would defer  
18 to a toxicologist or an oncologist, is  
19 what you just testified to, correct?

20 MS. THOMPSON: Objection to  
21 form.

22 THE WITNESS: The amount  
23 that would make it a carcinogen in  
24 animals, yes.

1 BY MR. VAUGHN:

2 Q. And in humans?

3 A. I don't have to defer to  
4 anybody on that one because it's never  
5 been studied, so it's not known.

6 Q. Okay. But at least in  
7 animals, you would defer to an oncologist  
8 or toxicologist on how much of a dose is  
9 necessary to induce cancer, correct?

10 MS. THOMPSON: Objection.  
11 Form.

12 THE WITNESS: Correct. As  
13 I've stated before, it was not the  
14 intent of my report to define that  
15 threshold.

16 My point was to find the  
17 threshold below which there  
18 doesn't appear to be a cancer  
19 risk.

20 BY MR. VAUGHN:

21 Q. Okay. So would you also  
22 defer to a cancer researcher on what dose  
23 would cause cancer or could increase the  
24 risk of cancer?

1 MS. THOMPSON: Objection.

2 Form.

3 THE WITNESS: That's what I  
4 said, yes.

5 BY MR. VAUGHN:

6 Q. All right. She objected.  
7 Let me ask it again so it's really clear.

8 In regards to the dose  
9 necessary for NDMA to increase the risk  
10 of cancer, you would defer to a cancer  
11 researcher, correct?

12 MS. THOMPSON: Objection.  
13 Form.

14 THE WITNESS: It's not the  
15 nature of my testimony.

16 BY MR. VAUGHN:

17 Q. And so you would defer to a  
18 cancer researcher, correct?

19 A. Potentially. Could be  
20 toxicologist. Could be somebody else.  
21 But it's not the nature of my testimony.

22 Q. Let's go to Page 33 of your  
23 report now.

24 So towards the bottom of



1 this page, you opine that the liver may  
2 have a carcinogenic surveillance system  
3 that removes O6 from DNA prior to  
4 carcinogenesis.

5 Is this opinion based on the  
6 Pegg paper that you cited above?

7 A. Pegg refers to it in his  
8 paper. There are many others that I came  
9 across that refer to that too. And the  
10 surveillance system is my own sort of  
11 selection of a descriptor.

12 Q. Do you find Pegg to be  
13 reliable?

14 A. Yes.

15 Q. Your opinion regarding the  
16 surveillance system being able to remove  
17 O6 from DNA prior to carcinogenesis, is  
18 that opinion specific to the liver?

19 A. In the context of what my  
20 report is, I'm referring to the liver's  
21 ability to protect itself against  
22 potential carcinogens from NDMA, again  
23 depending on the dose.

24 My understanding, although

1 it's not my area, is that that  
2 surveillance system is essentially in all  
3 tissues, in all cells.

4 Q. And so you agree that this  
5 surveillance system opinion is really not  
6 in your wheelhouse, correct?

7 MS. THOMPSON: Objection.

8 Form.

9 THE WITNESS: It's in my  
10 wheelhouse in the context of how I  
11 used it. I'm not trying to  
12 quantify it.

13 I find it from a  
14 pharmacologic sense interesting  
15 that the lower dose NDMA, because  
16 of first-pass metabolism and  
17 clearance, 2E1 produces the  
18 potential carcinogen in the very  
19 organ that has the best probable  
20 capacity to remove it.

21 BY MR. VAUGHN:

22 Q. And so if NDMA were to have  
23 a high bioavailability in humans and was  
24 able to get past the liver, the liver's

1 carcinogenic surveillance system wouldn't  
2 have any impact on the O6 formations in  
3 other organs or tissues, correct?

4 MS. THOMPSON: Objection.  
5 Form.

6 THE WITNESS: Again, that's  
7 a hypothetical. That's not what  
8 I'm dealing with because we're not  
9 giving those kinds of doses to  
10 humans.

11 BY MR. VAUGHN:

12 Q. You are an expert in this  
13 litigation, so I can ask you a  
14 hypotheticals.

15 And I'm saying  
16 hypothetically, if it were to get past  
17 the liver, the liver surveillance system  
18 wouldn't have any impact on those O6  
19 formations in other tissues and organs,  
20 correct?

21 MS. THOMPSON: Objection.  
22 Form.

23 THE WITNESS: Yeah, if you  
24 were to give some massive

1 overdose, then I guess, in theory,  
2 in your hypothetical, you could  
3 bypass the liver.

4 BY MR. VAUGHN:

5 Q. But you don't know what dose  
6 that is, correct?

7 A. I do not.

8 Q. Okay. Are you aware --  
9 sorry.

10 Are you aware of any factors  
11 that can inhibit or increase the  
12 metabolism of NDMA in the liver?

13 MS. THOMPSON: Objection.  
14 Form.

15 THE WITNESS: The only one  
16 that I looked at, because of my  
17 interest in pharmacogenomics, is  
18 to see if there is any 2E1 related  
19 polymorphisms. And those have not  
20 been identified. So no.

21 BY MR. VAUGHN:

22 Q. And so in coming to your  
23 opinions in this case, you did not  
24 consider any factors that could inhibit

1 or increase the metabolism of NDMA in the  
2 liver?

3 MS. THOMPSON: Objection.

4 THE WITNESS: In the  
5 research that I did, if I came  
6 across it, then I would have  
7 commented on it. So it wasn't  
8 that I didn't consider it. I  
9 would have looked for it in the  
10 articles that I was looking at.

11 BY MR. VAUGHN:

12 Q. And you didn't comment  
13 anywhere in your expert report on it, did  
14 you?

15 A. I did not.

16 Q. Did you actually read the  
17 Pegg paper?

18 A. I did.

19 MR. VAUGHN: Hey, Tyler, can  
20 you pull up the 1980 Pegg paper  
21 for us.

22 (Document marked for  
23 identification as Exhibit  
24 Bottorff-4.)

1 MR. VAUGHN: Go to PDF Page  
2 15.

3 BY MR. VAUGHN:

4 Q. All right. And that second  
5 sentence, can you read that aloud for the  
6 jury, please, where it starts, "For  
7 example."

8 A. "For example, when the  
9 ability of the liver to metabolize NDMA  
10 is impaired by feeding a  
11 protein-deficient diet, a greater  
12 fraction of the carcinogen may become  
13 available for reaction with other  
14 organs."

15 Q. Why did you not mention that  
16 in your expert report?

17 MS. THOMPSON: Objection.  
18 Form.

19 THE WITNESS: I have no  
20 reason for that. But again, the  
21 impact of that would have to also  
22 depend on the dose.

23 And so, I didn't consider it  
24 as having an impact on the doses

1           that we're talking about.

2       BY MR. VAUGHN:

3           Q.       Why didn't you mention that  
4       in your expert report? I thought you  
5       said you would have addressed it?

6           MS. THOMPSON: Objection.

7           Form.

8           THE WITNESS: Because I  
9       didn't think it would have an  
10      impact at the amount of doses that  
11      we are talking about.

12      BY MR. VAUGHN:

13           Q.       Well, that's not the answer  
14      that you gave me a second ago, is it?

15           MS. THOMPSON: Objection.

16           Form.

17      BY MR. VAUGHN:

18           Q.       Go ahead and read the next  
19      sentence. Starts also. "Also since  
20      uptake."

21                    Can you read that for the  
22      jury?

23           MS. THOMPSON: Can he answer  
24      the question that you had earlier

1 before we --

2 MR. VAUGHN: I'm sorry. I  
3 thought he -- yeah, absolutely.

4 MS. THOMPSON: Okay. We may  
5 need the court reporter to read it  
6 back. But I think you asked an  
7 question and then he didn't  
8 answer --

9 MR. VAUGHN: I can ask it  
10 again.

11 BY MR. VAUGHN:

12 Q. That was not the answer that  
13 you gave earlier, was it?

14 MS. THOMPSON: Objection.  
15 Form.

16 Go ahead.

17 THE WITNESS: And I think I  
18 said that if it would have  
19 impacted my opinions, I would have  
20 included it. And so it didn't  
21 impact my opinion.

22 BY MR. VAUGHN:

23 Q. I thought you said if you  
24 would have read it in the literature you



1 would have addressed it in your expert  
2 report.

3 MS. THOMPSON: Objection to  
4 form. Mischaracterizes.

5 THE WITNESS: If it would  
6 have impacted my opinion.

7 BY MR. VAUGHN:

8 Q. And again, you haven't  
9 reviewed all the internal testing on the  
10 levels of NDMA in valsartan, have you?

11 MS. THOMPSON: Objection.  
12 Form.

13 THE WITNESS: No, I haven't.

14 BY MR. VAUGHN:

15 Q. Okay. I'm going to now ask  
16 you if you can read that next sentence  
17 that starts with "Also, since uptake."

18 A. "Also, since uptake of NDMA  
19 is more rapid from the small intestine  
20 than from the stomach, agents that retard  
21 gastric emptying might be expected to  
22 slow the rate of absorption."

23 Q. What does "retard gastric  
24 emptying" mean?

1           A.       Slow gastric emptying into  
2       the site of absorption.

3           Q.       Okay. Can you read the next  
4       sentence for me?

5           A.       "Agrelo have recently  
6       published data which show that the  
7       presence of fat retards the rate of  
8       uptake and the metabolism of oral doses  
9       of NDMA."

10          Q.       And you --

11          A.       And he -- I'm sorry.

12                   Then he goes on to say that  
13       that might actually increase its  
14       metabolism by the liver, not enhance its  
15       ability to escape the liver.

16          Q.       And you didn't mention that  
17       in your report either, did you?

18                   MS. THOMPSON: Objection.

19                   Form.

20                   THE WITNESS: No. Again,  
21       these aren't things that I  
22       considered. He was being thorough  
23       in looking at potentials.

24                   But most of these would have

1 effects, based on my knowledge of  
2 these issues with other drugs that  
3 would not be -- that would not  
4 alter my opinion about NDMA in the  
5 doses that we are talking about.

6 BY MR. VAUGHN:

7 Q. Do you know if a person's  
8 liver would metabolize NDMA with the same  
9 efficiency if the person took their  
10 valsartan with just water versus taking  
11 their valsartan with food or drinks other  
12 than water?

13 MS. THOMPSON: Objection.  
14 Form.

15 THE WITNESS: I'm sorry,  
16 effect their absorption of what?

17 BY MR. VAUGHN:

18 Q. Do you know if a person's  
19 liver would metabolize NDMA at the same  
20 efficiency regardless if the patient took  
21 the valsartan with water or if they took  
22 it with food or if they took it with a  
23 drink other than water?

24 MS. THOMPSON: Object to

1 form.

2 THE WITNESS: We -- sorry.

3 We don't know that.

4 BY MR. VAUGHN:

5 Q. We don't -- who is we?

6 A. We, us, all of us. Nobody  
7 knows that answer.

8 Q. Are you speaking for the  
9 plaintiffs' experts as well?

10 A. Well, let me rephrase my  
11 answer then.

12 There are no data in humans  
13 that address that question that you  
14 asked.

15 Q. What about animals?

16 A. I mean, you could talk about  
17 what he says here. I don't think they  
18 have a substantial effect at the doses  
19 we're talking about.

20 Q. What do you base that on?

21 A. Just that these doses are so  
22 small and generally these sort of  
23 theoreticals don't have that much of an  
24 impact.

1 Q. And again, these doses that  
2 are so small, you're not even aware of  
3 the highest doses, are you?

4 MS. THOMPSON: Objection.  
5 Form. Asked and answered.

6 THE WITNESS: I'm aware of  
7 the highest doses that I had  
8 access to.

9 BY MR. VAUGHN:

10 Q. Do you know if vitamins can  
11 impact the carcinogenicity of NDMA or  
12 NDEA in animals or humans?

13 MS. THOMPSON: Objection to  
14 form.

15 THE WITNESS: I have not  
16 looked at that.

17 BY MR. VAUGHN:

18 Q. Being a vegetarian, would  
19 that have any impact on how efficiently  
20 someone's liver can metabolize NDMA?

21 MS. THOMPSON: Objection to  
22 form.

23 THE WITNESS: I have no  
24 opinion on that.

1 BY MR. VAUGHN:

2 Q. Same thing with a high-fat  
3 diet. You have no opinion on that if  
4 it's going to impact the rate of  
5 metabolism of NDMA in a human liver?

6 A. I have no -- no opinion.

7 Q. Same with alcohol, no  
8 opinion on if that's going to impact the  
9 metabolism of NDMA in a human?

10 A. Correct.

11 Q. So is your opinion regarding  
12 NDMA in valsartan, how it's going to be  
13 metabolized, based on the assumption that  
14 nothing else can impact the metabolism?

15 MS. THOMPSON: Objection.  
16 Form.

17 THE WITNESS: Let me put it  
18 back into perspective that as my  
19 approach.

20 Again, in the doses that do  
21 not appear to be carcinogenic in  
22 animals, which is hovering around  
23 .1 milligrams per kilogram or  
24 lower, that that threshold, which

1 is not the carcinogenic threshold,  
2 it's the non-carcinogenic  
3 threshold, is in the range of 350  
4 to 21,000 times higher than the  
5 valsartan I evaluated as having  
6 contained those amounts of NDMA.

7 And so, if gastric emptying  
8 or taking a glass of water versus  
9 a glass of milk, there's never  
10 been any bioavailability study  
11 with any drug under any of those  
12 conditions that has changed  
13 absorption by 350 times or, you  
14 know, 22,000 times.

15 So these issues that  
16 might -- in Pegg's paper where I  
17 think he was being thorough in all  
18 the data he analyzed, in my  
19 opinion, having read this, it had  
20 no impact on my conclusion.

21 So I didn't put it in the  
22 paper for that reason.

23 BY MR. VAUGHN:

24 Q. Your paper is not as

1 thorough as Pegg's?

2 MS. THOMPSON: Is that a  
3 question or a statement?

4 MR. VAUGHN: It's a  
5 question.

6 MS. THOMPSON: Objection.  
7 Form.

8 THE WITNESS: My paper is  
9 focused on what I focused on. His  
10 paper focused on other things.

11 BY MR. VAUGHN:

12 Q. In your opinion, is  
13 100 percent of NDMA absorbed and makes  
14 its way to the liver?

15 MS. THOMPSON: Objection.  
16 Form.

17 THE WITNESS: Do you mean  
18 given orally?

19 BY MR. VAUGHN:

20 Q. Correct.

21 A. Because inhaled --

22 Q. No, I understand. I  
23 appreciate your clarification. I'll  
24 re-ask the question.



1                   Is it your opinion that when  
2 NDMA is ingested orally, that 100 percent  
3 of it makes its way to the liver?

4                   A.       Yes. I think there are  
5 bioavailability studies in animals that  
6 show that.

7                   Q.       So none of it is going to be  
8 excreted through the feces or make it  
9 down that tract?

10                  A.       No. I think the study I  
11 saw, the absorption was 90-something  
12 percent.

13                  Q.       Does the stomach have P450  
14 in it?

15                  A.       It does. The only two  
16 enzymes that I've seen in the stomach are  
17 like 2J2 and 2S4, or something.

18                            So very, very, very uncommon  
19 P450s, but not the ones we are talking  
20 about.

21                  Q.       What about in the  
22 intestines, large intestine, small  
23 intestine? Do they have P450-2E1?

24                  A.       Actually, they do not. The

1 small intestine does not have 2E1.

2 Q. A second ago, did you say  
3 that you saw a study that said 90 percent  
4 was absorbed?

5 A. I believe that's the one  
6 that I saw where they gave administration  
7 through a feeding tube into the stomach  
8 and then also down into the intestine.

9 Q. So that's not 100 percent.  
10 Where's that other ten percent going?

11 MS. THOMPSON: Objection.  
12 Form.

13 THE WITNESS: They just  
14 couldn't measure it anymore from  
15 drawing back from the tube.

16 BY MR. VAUGHN:

17 Q. Is there a chance that some  
18 of it would be excreted to the feces?

19 A. It hasn't been described.

20 Q. Do you know if the rectum  
21 has P450-2E1?

22 A. I believe it does not. My  
23 understanding is that as you go further  
24 down from the small intestine towards the

1 larger intestine, that there's this  
2 decline in all the P450s. And I have  
3 never seen anything that identified 2E1  
4 being in the colon or rectum.

5 Q. Does the entire GI tract  
6 have P450 in it?

7 MS. THOMPSON: Objection.

8 Form.

9 THE WITNESS: Some have  
10 P450, and some do not.

11 BY MR. VAUGHN:

12 Q. The study in which you were  
13 saying 90 percent, what animal was that  
14 in? Do you recall?

15 A. Pretty sure it was in rats.

16 Q. And was that an oral dose?

17 A. Yes. They put like a  
18 feeding tube down and then administered  
19 the NDMA through the feeding tube. And  
20 then sampled back out of the feeding tube  
21 over time to see how the drug was  
22 absorbed.

23 Q. How does pulling it back out  
24 let you know if it made it to the liver?

1 MS. THOMPSON: Objection.

2 Form.

3 THE WITNESS: There are  
4 other studies showing that it goes  
5 to the liver once it's absorbed in  
6 the small intestine.

7 MR. VAUGHN: Can we go to  
8 Page 19 -- actually, before we do  
9 that, stay here.

10 Can we go to the bottom of  
11 the summary of -- on this page,  
12 yeah.

13 BY MR. VAUGHN:

14 Q. Then can you read the  
15 sentence that starts with, "The greatest  
16 capacity," and read that sentence and the  
17 one afterward.

18 A. Yeah, I can see fine on  
19 mine.

20 "The greatest capacity to  
21 metabolize these nitrosamines to  
22 alkylating agents is found in the liver,  
23 but other organs including the esophagus,  
24 lung and kidney are also capable of

1 activation."

2 Q. And the next sentence as  
3 well, please.

4 A. "These organs may be more  
5 susceptible to alkylation than the liver  
6 because they have a lesser ability to  
7 catalyze the removal of the  
8 O6-alkyl-guanine from their DNA."

9 Q. Do you agree with that?

10 A. Particularly if you go on to  
11 the next sentence, because I want to put  
12 it in the proper context.

13 "However, orally  
14 administered doses of NDMA and the NDMA  
15 formed by nitrosation reactions" --

16 THE WITNESS: Can you keep  
17 scrolling for me, please.

18 MS. THOMPSON: I don't have  
19 control of the documents.

20 THE WITNESS: Oh, I'm sorry.

21 -- "within the GI tract are  
22 rapidly absorbed from the upper  
23 part of the small intestine and  
24 carried to the liver in the portal

1 blood supply. When small doses  
2 are given in this way, the  
3 capacity of the liver to  
4 metabolize the carcinogen is  
5 sufficient that the nitrosamines  
6 effectively cleared in a  
7 first-pass effect, leaving very  
8 little to interact with other  
9 organs."

10 So to read those couple  
11 sentences that you had me start  
12 with, I think it was only fair to  
13 put it into the context of the  
14 rest of Pegg's comments.

15 BY MR. VAUGHN:

16 Q. No, actually. I'm really  
17 glad that you did. At the end of that,  
18 it said "very little is left to interact  
19 with other organs."

20 You agree with that, right?  
21 It's not that it's none left. It's just  
22 not as much, right?

23 A. No, not right. It depends  
24 on the dose.

1 Q. And here it says "when small  
2 doses are given." Would you agree with  
3 that? Small doses, you're still going to  
4 get a little bit that goes to the other  
5 organs?

6 A. Depends on --

7 MS. THOMPSON: Objection to  
8 form.

9 Sorry.

10 THE WITNESS: Sorry.

11 It depends on how small the  
12 dose.

13 BY MR. VAUGHN:

14 Q. Do you have any idea what  
15 Pegg meant when he said small dose here?

16 A. No, he didn't define it in  
17 this set.

18 Q. And we don't know if his  
19 definition of small dose is the same as  
20 your definition of a trace amount?

21 A. I don't.

22 Q. All right. Can we go back  
23 to your expert report, and go to Page 19  
24 now.

1 Can you read out loud the  
2 first full sentence on this page? It  
3 starts at the end of Line 117.

4 MS. THOMPSON: Line 117?

5 MR. VAUGHN: I messed up on  
6 that. 317.

7 It starts with the word  
8 "only." Sorry about that.

9 MS. THOMPSON: Here, if it's  
10 easier to read.

11 THE WITNESS: I've go it.

12 "Only when the dose exceeds  
13 first-pass metabolism capacity  
14 will unchanged drug or compound be  
15 systemically available for  
16 distribution through the  
17 bloodstream, leaving the liver and  
18 being delivered to other tissues  
19 and organs."

20 BY MR. VAUGHN:

21 Q. And so is it your opinion  
22 that if a human orally ingests NDMA, that  
23 it would only be detectable in the blood  
24 if it was exceeding the first-pass



1 metabolism capacity of the liver?

2 A. Correct.

3 Q. Do you agree that if NDMA  
4 reaches the bloodstream, that it has the  
5 potential to cause cancer in numerous  
6 organs and tissues?

7 MS. THOMPSON: Objection.

8 Form.

9 THE WITNESS: Again, I think  
10 we've talked about this a few  
11 times.

12 It depends on the amount,  
13 how much gets past the liver. And  
14 the ability of that organ to  
15 generate -- or to have the 2E1.

16 So it's dependent on a lot  
17 of things.

18 BY MR. VAUGHN:

19 Q. And again, you've stated  
20 several times that you're not here to  
21 talk about what dose is necessary.

22 So dose aside, if you're  
23 getting into the bloodstream there's more  
24 organs and tissues at risk, correct?

1 MS. THOMPSON: Object to  
2 form.

3 THE WITNESS: There's --  
4 there's more organs and tissue  
5 that can receive the drug. I  
6 don't know what that risk is  
7 because it depends on the amount.

8 BY MR. VAUGHN:

9 Q. I mean, the risk of it would  
10 be getting cancer. Are you saying that  
11 you don't know how likely they are to get  
12 cancer?

13 A. Yes.

14 MS. THOMPSON: Object to  
15 form.

16 THE WITNESS: I can't  
17 quantify without having a dose  
18 to -- or an amount that gets to  
19 the organ or knowing which organ  
20 and how much 2E1 it has and how  
21 much of a removal system that it  
22 has.

23 Those are -- those are all  
24 things that would impact the

1 conclusion you were drawing.

2 BY MR. VAUGHN:

3 Q. Are you aware if some people  
4 are exposed to NDMA in their diet?

5 A. I am aware of that.

6 Q. Do you know what the average  
7 amount of NDMA that -- scratch that. One  
8 second.

9 Do you know what the average  
10 amount of NDMA an American is exposed to  
11 in their diet every day?

12 MS. THOMPSON: Objection to  
13 form.

14 THE WITNESS: I recall  
15 having seen it.

16 My recollection is that it  
17 might be like a few hundred  
18 nanograms or up to maybe a tenth  
19 of a microgram or something like  
20 that.

21 BY MR. VAUGHN:

22 Q. It's kind of impossible to  
23 not be exposed to NDMA at all as a human,  
24 correct?

1           A.       I would say that the sources  
2 of NDMA that I've read about that are in  
3 dietary substances, some or many of them  
4 are part of the normal American diet,  
5 yes.

6           Q.       Is it your opinion that NDMA  
7 in the diet can't cause cancer in humans?

8                   MS. THOMPSON:   Objection to  
9 form.

10                   THE WITNESS:   It is my  
11 opinion that looking at the  
12 dietary studies that have been  
13 done, I don't believe they  
14 reliably and consistently show  
15 that they have caused cancer  
16 through dietary studies.

17 BY MR. VAUGHN:

18           Q.       But they do show an  
19 association, correct?

20                   MS. THOMPSON:   Objection to  
21 form.

22                   THE WITNESS:   Sorry.   An  
23 association, yes.

24 BY MR. VAUGHN:

1 Q. I want to ask you again your  
2 opinion. Can the amount of NDMA in the  
3 diet increase the risk of cancer in  
4 humans?

5 MS. THOMPSON: Objection to  
6 form.

7 THE WITNESS: And I'm saying  
8 that hasn't been demonstrated. If  
9 it had been, it would have a  
10 different IARC classification than  
11 it does.

12 BY MR. VAUGHN:

13 Q. You're saying the amount of  
14 NDMA in the diet probably could increase  
15 the risk of cancer in humans?

16 A. No, I'm not saying that.  
17 I'm saying there's no data that it does  
18 increase cancer in humans.

19 Q. There's no data at all?

20 A. There are no data that prove  
21 that NDMA in the diet causes cancer in  
22 humans.

23 Q. And so prove. Again, like,  
24 you're putting this at 100 percent

1 standard, right?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: I don't  
5 believe it's been proven. The  
6 preponderance of the data are  
7 conflicting to me.

8 BY MR. VAUGHN:

9 Q. Does it lean more one way or  
10 the other?

11 MS. THOMPSON: Objection to  
12 form.

13 THE WITNESS: Not in any  
14 type of reliable conclusion that  
15 I've been able to make, no.

16 BY MR. VAUGHN:

17 Q. So I'm okay to start eating  
18 a lot of bacon with my whiskey again?  
19 It's not going to increase my risk of  
20 cancer?

21 MS. THOMPSON: Objection to  
22 form.

23 BY MR. VAUGHN:

24 Q. I'd like to be able to do

1     that again.   That's -- I really like  
2     bacon.

3             A.     On your grilled hamburger,  
4     yes.

5                     MR. VAUGHN:   Do you want to  
6     take a break real quick.   Is that  
7     okay?

8                     MS. THOMPSON:   Sure.

9                     THE VIDEOGRAPHER:   The time  
10    right now is 2:07 p.m.   We're off  
11    the record.

12                    (Short break.)

13                    THE VIDEOGRAPHER:   The time  
14    right now is 2:23 p.m.   We're back  
15    on the record.

16    BY MR. VAUGHN:

17             Q.     Doctor, if a human is able  
18    to exceed their body's repair mechanisms  
19    just through NDMA in their diet, then  
20    wouldn't any additional amount of NDMA  
21    further increase their risk of cancer?

22                    MS. THOMPSON:   Objection.  
23    Form.

24                    THE WITNESS:   Again, I

1           suspect that's theoretically  
2           possible, but --

3       BY MR. VAUGHN:

4           Q.       What do you mean theoretical  
5           possible?

6           A.       Well they would have to --  
7           well, number one, there's no proof in  
8           humans that dietary NDMA causes cancer.

9                   And so it's operating from  
10          the assumption that it does, and so it  
11          makes it hard for me to accept that  
12          hypothetical.

13          Q.       If an animal is able to  
14          exceed their body's repair mechanisms  
15          just through the NDMA in their diet, then  
16          wouldn't any additional amount of NDMA  
17          further increase that animal's risk of  
18          cancer?

19                   MS. THOMPSON:   Objection.  
20                   Form.

21                   THE WITNESS:   So again, the  
22                   basis for that question was that  
23                   dietary NDMA is causing cancer in  
24                   animals?



1 BY MR. VAUGHN:

2 Q. Yeah. If/then. It's a  
3 hypothetical?

4 A. I mean, same thing, it would  
5 have to be enough to cause cancer to  
6 begin with.

7 Q. And, again, hypothetical.  
8 If that was enough, then any additional  
9 amount of NDMA would further increase the  
10 risk of cancer, correct?

11 MS. THOMPSON: Objection.  
12 Form.

13 THE WITNESS: Well, I  
14 believe the dose studies that have  
15 given enough to cause cancer sort  
16 of prove that that's possible.

17 BY MR. VAUGHN:

18 Q. Thank you, Doctor. Now, a  
19 second ago you said the average amount  
20 diet would have a few hundred nanograms  
21 of NDMA in it a day. But what about a  
22 single meal? Do you know how much that  
23 on average would have?

24 MS. THOMPSON: Objection to

1 form. Scope.

2 THE WITNESS: I don't.

3 BY MR. VAUGHN:

4 Q. Less than a few hundred  
5 nanograms, though, right?

6 MS. THOMPSON: Objection.

7 Form. Scope.

8 THE WITNESS: I mean, I  
9 guess it depends on the meal  
10 relative to the other meals of the  
11 day. I mean, I don't know.

12 MR. VAUGHN: Tyler, can we  
13 pull Pegg back up again, the 1980  
14 Pegg study. Let's go to Page 15  
15 again.

16 BY MR. VAUGHN:

17 Q. Doctor, that second  
18 paragraph that starts with the word  
19 "finally," can you read that aloud for  
20 the jury?

21 A. "Finally, it has been  
22 reported that NDMA and NDEA were present  
23 in human peripheral blood samples and  
24 that the amounts increased after a meal.

1 Calculations of total daily exposures  
2 have been made on the basis of these  
3 figures but without knowledge of the  
4 clearance rate these calculations may be  
5 seriously in error and may underestimate  
6 total exposure."

7 Q. And so this is saying just  
8 one meal is able to clear the liver and  
9 get into the bloodstream, the NDMA; is  
10 that correct?

11 MS. THOMPSON: Objection.  
12 Form.

13 THE WITNESS: Again, I'd  
14 have to look at those studies to  
15 see if just that one-sentence  
16 summary would be an accurate  
17 representation.

18 BY MR. VAUGHN:

19 Q. Did you not look at those  
20 two studies when you were forming the  
21 basis of your opinions?

22 A. No, I did not.

23 Q. And so if this is true, that  
24 a meal can -- levels of NDMA in a meal

1 can exceed what the liver can handle and  
2 make it into the bloodstream, then if  
3 someone took valsartan with NDMA in it,  
4 that would also be able to make it into  
5 the bloodstream, correct?

6 MS. THOMPSON: Objection.

7 Form.

8 THE WITNESS: Again, I can't  
9 draw that same conclusion without  
10 looking at those studies.

11 BY MR. VAUGHN:

12 Q. And you didn't look at those  
13 studies, so you can't really opine on  
14 what impact dietary NDMA is going to have  
15 on the NDMA that's in valsartan, correct?

16 MS. THOMPSON: Objection.

17 Form.

18 THE WITNESS: No, I haven't  
19 looked at these studies. So I  
20 can't tell you what impact they  
21 would have on my opinions.

22 BY MR. VAUGHN:

23 Q. What were the levels that  
24 you were aware of, of NDMA in valsartan?

1 Was it 20,000 nanograms and they were  
2 able to show 38,000 nanograms? Is that  
3 what it says?

4 A. Yes.

5 Q. All right. And you said  
6 that the average diet would have a few  
7 hundred nanograms. But yet one meal is  
8 able to bypass the liver and the NDMA get  
9 into the bloodstream?

10 A. I don't know that. I  
11 haven't read these studies. They weren't  
12 what I looked at in looking at NDMA  
13 metabolism.

14 Q. If just a couple hundred  
15 nanograms can bypass the liver, then, I  
16 mean, tens of thousands of nanograms of  
17 NDMA would definitely bypass the liver,  
18 correct?

19 MS. THOMPSON: Objection to  
20 form.

21 THE WITNESS: I can't answer  
22 that without looking at these  
23 studies.

24 BY MR. VAUGHN:

1 Q. It's a hypothetical. It's  
2 an if/then. If a few hundred was able to  
3 bypass, then definitely tens of  
4 thousands, correct?

5 MS. THOMPSON: Objection to  
6 form.

7 THE WITNESS: Well, again,  
8 you're asking me to accept the  
9 "if." And I have to look at these  
10 studies before I would accept  
11 that.

12 BY MR. VAUGHN:

13 Q. Because you didn't review  
14 all the literature before you formed your  
15 opinions in this case or before this  
16 deposition, right?

17 MS. THOMPSON: Objection.  
18 Form.

19 THE WITNESS: I was not  
20 focused on dietary NDMA.

21 BY MR. VAUGHN:

22 Q. Are you going to review  
23 these studies after this deposition?

24 A. I could.

1 Q. And if you change your  
2 opinions, are you going to notify us?

3 A. If I change my opinions, I  
4 would notify you.

5 MS. THOMPSON: You will  
6 notify us, and we will notify.

7 THE WITNESS: Well.

8 BY MR. VAUGHN:

9 Q. Doctor, can you explain how  
10 you did your dosage conversions around  
11 animal to human?

12 A. I just used milligrams per  
13 kilogram. And the average typically used  
14 weight for a human is 70 kilograms.

15 Q. Based on what authority did  
16 you decide that the -- scratch that one  
17 second.

18 The average typically used  
19 weight for a human is 70 kilograms. What  
20 did you base that off of?

21 A. That's been a historical  
22 number that you can find in the  
23 literature for literally decades.

24 Q. So it's not like a standard

1 of practice in pharmacy and stuff that  
2 you would use 70 kg for a human?

3 MS. KAPKE: Object to form.

4 THE WITNESS: Sorry. Not  
5 any more standard to pharmacy than  
6 it is to any of the other health  
7 professions.

8 BY MR. VAUGHN:

9 Q. Including oncology?

10 A. Including oncology,  
11 including cardiology, nephrology. That's  
12 been in the literature as sort of a  
13 standard for a long time, probably longer  
14 than what would be accurate today. I  
15 think the number today would probably be  
16 even bigger.

17 Q. It's important to have that  
18 number be accurate, correct?

19 A. In a comparative basis, not  
20 necessarily. But you know, it's ballpark  
21 enough to make the point.

22 Q. And so you don't know -- you  
23 said that cancer research oncologists,  
24 they all use 70 kg, right?



1 MS. THOMPSON: Object to  
2 form.

3 THE WITNESS: I didn't say  
4 that. I said it's been accepted  
5 by all branches of the medical and  
6 pharmacy and nursing communities  
7 when people are sort of talking  
8 about what the average human  
9 weight is. And that's been around  
10 for decades.

11 BY MR. VAUGHN:

12 Q. Did you do any research to  
13 make sure that that's the weight that's  
14 used when you're dealing with a  
15 carcinogen?

16 MS. THOMPSON: Objection.  
17 Form.

18 THE WITNESS: No, I did not.

19 BY MR. VAUGHN:

20 Q. You just assumed that you  
21 would use the same weight?

22 MS. THOMPSON: Objection.  
23 Form.

24 THE WITNESS: Again, it's

1 for a relative basis.

2 If I were to use 10  
3 kilograms less or 10 kilograms  
4 more, or 20 kilograms more, it  
5 wouldn't change my opinions.

6 BY MR. VAUGHN:

7 Q. Isn't it your opinion that  
8 the levels of NDMA present in generic  
9 valsartan don't increase the risk of  
10 cancer for anyone taking it?

11 MS. THOMPSON: Objection.  
12 Form.

13 THE WITNESS: Could you  
14 rephrase that again for me,  
15 please?

16 BY MR. VAUGHN:

17 Q. Yeah.

18 Is it your opinion that the  
19 levels of NDMA that were present in  
20 generic valsartan did not pose an  
21 increased risk of cancer formation for  
22 anyone that took the drug?

23 A. Yes. That's in my report.

24 Q. If your opinion is on anyone

1 that took the drug, why are you using  
2 average human weight?

3 A. For comparative purposes. I  
4 guess I could have used, if I had them,  
5 the weights of all the people who took  
6 the drug. But I didn't have that.

7 Q. I mean, wouldn't  
8 approximately half of humans weigh less  
9 than the actual weight of a human?

10 A. Yes.

11 Q. If you were so confident in  
12 your opinions that the levels of NDMA in  
13 valsartan can't cause or increase the  
14 risk of human cancer, why didn't you just  
15 go with the lowest weight value. Why did  
16 you use average?

17 MS. THOMPSON: Objection.

18 Form.

19 THE WITNESS: I don't know  
20 what the lowest weight would have  
21 been. But had I picked, you know,  
22 60 kilograms or 20 or -- I don't  
23 know what you mean, because I  
24 don't know what that number is.

1 BY MR. VAUGHN:

2 Q. Well, it significantly  
3 impacts your calculation, does it not?

4 MS. THOMPSON: Objection.  
5 Form.

6 THE WITNESS: No. It really  
7 doesn't. If you look at my table,  
8 you know, where I use the 70-kilo,  
9 and get 7,000 milligrams, as what  
10 appeared to be a non-cancerous  
11 dose based on a .1 milligram per  
12 kilogram in rat studies, whether  
13 that number is 6,000 or in the  
14 case of someone who's larger,  
15 whether that number is 15,000, it  
16 doesn't change my opinions.

17 BY MR. VAUGHN:

18 Q. All right. Based on your  
19 methodology, if 1 nanogram of NDMA was  
20 able to induce cancer in an animal that  
21 weighed one kilogram, then based on your  
22 calculations, it would take 70 nanograms  
23 to induce cancer in a human; is that  
24 correct?

1           A.       Well, I never calculated  
2     that.

3           Q.       Well, I know you didn't do  
4     this calculation. But the way you're  
5     doing your conversion -- and so I'm not  
6     trying to represent that one nanogram  
7     causes cancer in animals. I'm just using  
8     these numbers for simplicity's sake  
9     because I want to understand your  
10    methodology and how you came to these  
11    numbers.

12                   Does that make sense?

13           A.       Yeah, we can just use the  
14    numbers and use them. We don't have to  
15    use something other than the numbers.

16           Q.       Well, I need the math to be  
17    a lot easier, is why I'm doing it this  
18    way.

19           A.       Okay. This is pretty easy.

20           Q.       So you're just taking  
21    whatever the nanograms per kilogram are  
22    and you're timesing them by 70, correct?

23           A.       And they're actually  
24    micrograms and/or milligrams, and not in

1 the nanogram range.

2 Q. Would you be more  
3 comfortable if I gave my hypothetical in  
4 micrograms instead of nanograms? Would  
5 that make it easier for you?

6 A. Well, like I said, we can  
7 just use the numbers. They're not that  
8 complicated. .1 --

9 Q. I'm allowed to ask you  
10 hypotheticals. And if I use basic  
11 numbers it's a lot easier for the jury to  
12 understand what your methodology is.

13 So if 1 microgram of NDMA  
14 was able to induce cancer in an animal  
15 that weighed 1 kilogram, based on your  
16 calculations, it would take 70 micrograms  
17 to induce cancer in a human; is that  
18 correct?

19 MS. THOMPSON: Objection.  
20 Form.

21 THE WITNESS: Again, if that  
22 were the case, which isn't the  
23 case.

24 BY MR. VAUGHN:

1 Q. But the way I did my math  
2 was how you did your methodology,  
3 correct?

4 A. Well, multiplying by 70,  
5 yes.

6 Q. Okay. And so for every kg,  
7 you added 100 percent of that base dose,  
8 correct?

9 A. For a dose that did not  
10 cause cancer in rats, that in a few  
11 studies was fairly consistent  
12 around .1 milligrams per kilogram, I  
13 extrapolated that to the average weight  
14 of a human adult, which is 70 kilograms.  
15 So 70 times the .1 gave 7 milligrams,  
16 which is 7,000 micrograms.

17 Q. Thank you, Doctor.

18 And so, if an animal weighs  
19 70 times as much as another animal, based  
20 on your methodology, it's going to take  
21 70 times the amount of NDMA to have the  
22 same impact on that animal, correct?

23 MS. THOMPSON: Objection.

24 Form.

1 THE WITNESS: I don't think  
2 that's what I'm saying here.

3 BY MR. VAUGHN:

4 Q. Can you explain to me what  
5 you're saying then?

6 A. Well, you again, reverted  
7 from the dose I said that doesn't cause  
8 cancer to a dose that does cause cancer,  
9 and I'm not claiming to know what that  
10 is.

11 Q. Okay. Let's set aside  
12 causing cancer. One nanogram per  
13 kilogram would be the same as 70  
14 nanograms for 70 kilograms.

15 That's what your math came  
16 out to be, right?

17 A. Correct. That's the math.

18 Q. Okay. And is that known as  
19 linear extrapolation?

20 MS. THOMPSON: Objection to  
21 form.

22 THE WITNESS: I don't know  
23 if that's the term that's used.  
24 But that would describe it



1 accurately, I think.

2 BY MR. VAUGHN:

3 Q. So it's like a one to one  
4 ratio, right? Like, for every kg, you  
5 add one part of the base, right?

6 A. Yeah. As long as it's  
7 reported in kilograms.

8 Q. And what was your basis that  
9 that one-to-one ratio was appropriate to  
10 use for NDMA?

11 A. It's just the best that we  
12 have. We don't have any other method of  
13 conversion based on some other  
14 physiologic factor. It's how the animals  
15 were dosed. They were dosed in  
16 milligrams per kilogram.

17 Q. But you have no basis for  
18 why that's appropriate to extrapolate  
19 them to humans based on weight?

20 A. Well, as I've already said,  
21 we are not sure that extrapolating these  
22 animal data to humans is accurate and the  
23 right thing to do to begin with.

24 So we have some missing

1 parts. We've got the milligram per  
2 kilogram dose in the animals, what dose  
3 didn't cause cancer, we have the weight,  
4 the average weight of a human adult, and  
5 then we have how much microgram  
6 quantities were in the valsartan product.

7 So there's that missing link  
8 connection that is an assumption that is  
9 being made.

10 Q. Okay. Let's set humans  
11 aside then.

12 If two different animal  
13 species, each weighed one kilogram, you  
14 would expect the exact same amount of  
15 NDMA to be necessary to induce cancer in  
16 those animals, correct?

17 A. No.

18 Q. Why?

19 A. Different amounts of 2E1.

20 Q. Does a rat and a mouse have  
21 different amounts of 2E1?

22 A. I believe they do. I know  
23 for sure a rat and a dog do and a rat and  
24 a monkey does and a rat and a pig does.

1 Q. But you don't know if a rat  
2 and a mouse have different amounts?

3 A. I don't recall seeing that.  
4 And the reason I do know about the  
5 monkeys and the pigs and the beagle dogs,  
6 is because there were studies that I  
7 reviewed that were in that area.

8 Q. And so you didn't consider  
9 the amount of 2E1 in mice when forming  
10 your opinions in this case?

11 A. No, I did not.

12 Q. Based on what you just said  
13 about the 2E1, assuming that they have  
14 comparable amounts of 2E1. An animal  
15 that weighs, let's say, 12 times as much  
16 as another animal, you would expect it to  
17 take 12 times the amount of NDMA to have  
18 the same impact, correct?

19 A. Well, I'm saying the dose  
20 would be. I am not saying what the  
21 impact would be. There's other parts to  
22 the question about causing cancer. And  
23 it has to do with the amount of 2E1 in  
24 the different organs and what the dose is

1 and whether you exceed first-pass  
2 metabolism, and do you give it IV or PO.

3 There's all these moving  
4 parts to the puzzle to even get close to  
5 having an apples-to-apples kind of  
6 comparison.

7 Q. Well, assuming that you're  
8 giving it the same route, you know,  
9 giving it orally for each of them.

10 A. Right. But again, they have  
11 different amounts of 2E1.

12 Q. I said assuming that they  
13 had comparable amounts of 2E1. I mean,  
14 you're assuming that human and rats have  
15 comparable amounts, right?

16 A. Well, that's been  
17 demonstrated. And I can't say it across  
18 all species.

19 Q. You don't know if mice have  
20 anything similar?

21 A. I just didn't look at that,  
22 no.

23 Q. You listed, "2018 M7(R1)  
24 Assessment and Control of DNA" --

1 reactivity -- "Reactive Impurities in  
2 Pharmaceuticals to Limit Potential  
3 Carcinogenic Risk: A Guidance For the  
4 Industry."

5 Did you read that entire  
6 document?

7 A. I did.

8 Q. And did you consider the  
9 2018 guidance for the industry in forming  
10 your opinions?

11 A. I considered them. But they  
12 didn't have an impact on my opinions.

13 Q. Do you recall disagreeing  
14 with anything from the 2018 guidance for  
15 industry?

16 A. It doesn't mean that I  
17 disagreed with them. It just means that  
18 they didn't have an impact on the  
19 conclusions that I drew based on NDMA  
20 metabolism relative to the amounts of  
21 NDMA found in the valsartan products.

22 Q. But what I was asking is do  
23 you recall disagreeing with anything in  
24 the guidance?

1           A.       I don't recall being in any  
2 position to disagree with it. I just was  
3 familiar with it.

4           Q.       And would you follow a  
5 guidance document like that?

6                   MS. THOMPSON: Objection.  
7 Form.

8                   THE WITNESS: I read the  
9 guidance document. I don't know  
10 what you mean by follow.

11                  MR. VAUGHN: Tyler, you can  
12 go ahead and pull that up for me.  
13 The 2018 M7(R1).

14                   (Document marked for  
15 identification as Exhibit  
16 Bottorff-5.)

17 BY MR. VAUGHN:

18           Q.       Guidance for industry.  
19 Who's the industry that this is supposed  
20 to guide?

21           A.       Pharmaceutical industry.

22           Q.       That's who you represent,  
23 correct?

24           A.       Correct.

1 Q. And at the bottom here, what  
2 agencies are responsible for this  
3 guidance document?

4 A. HHS, FDA, the CDER, CBER,  
5 which are branches of the FDA.

6 Q. So the U.S. Department of  
7 Health And and Human Services, the Food &  
8 Drug Administration, the Center for Drug  
9 Evaluation & Research, and the Center For  
10 Biologic Evaluation & Research; is that  
11 correct?

12 A. Yes. Just to clarify, CDER  
13 and CBER are branches of the FDA, and the  
14 FDA is a branch of the Health & Human  
15 Services.

16 Q. Okay. So this guidance  
17 document is basically put out by the U.S.  
18 Department of Health & Human Services?

19 A. Under the auspices of the  
20 FDA, and it's two specific branches that  
21 did the work.

22 Q. And what year was this put  
23 out?

24 A. 2018.

1 Q. And when did the industry --  
2 or not the industry. Scratch that.

3 When did the FDA  
4 approximately learn about the valsartan  
5 contamination with NDMA?

6 MS. THOMPSON: Objection.

7 Form.

8 THE WITNESS: I think it was  
9 in July of 2018 that they  
10 announced. I can't remember the  
11 exact date. But it was in 2018.

12 MR. VAUGHN: Go to Page 39,  
13 Tyler. Actually, one second. One  
14 second. Page 24. Can you go back  
15 two pages actually, Tyler, for me.  
16 I'm sorry. I got my PDF stuff  
17 wrong. That works. All right.  
18 Got it. Sorry. I'm having a hard  
19 time seeing it. Go -- no, no.

20 BY MR. VAUGHN:

21 Q. Do you see here what kg body  
22 weight they are using?

23 A. 50.

24 Q. And you used 70, correct?



1 A. Correct.

2 MS. THOMPSON: I think I'm  
3 in the wrong document. Is this in  
4 the shared file?

5 MR. VAUGHN: I mean, it's in  
6 his materials considered that you  
7 gave us.

8 MS. THOMPSON: I understand.  
9 I'm just trying to make sure that  
10 I'm pulling up the right one  
11 because the last exhibit that I  
12 have in here is Exhibit 5, which  
13 looks like it's the guidance  
14 document.

15 MR. VAUGHN: The first page  
16 says "Guidance for Industry.  
17 M7(R1)." It's March 2018.

18 BY MR. VAUGHN:

19 Q. So would you agree with me,  
20 Doctor, when the FDA is doing their  
21 calculations on carcinogens, they use a  
22 50 kg weight, not 70 kg rate?

23 MS. THOMPSON: Objection to  
24 form.

1 THE WITNESS: They did use  
2 50.

3 BY MR. VAUGHN:

4 Q. And do you know if they  
5 always use 50 when it's a carcinogen?

6 A. I do not know that. I think  
7 they -- I don't know if it's here or  
8 somewhere else that they explained their  
9 use of the 50 kilos, so they would be in  
10 their calculations on the  
11 ultra-conservative side.

12 Q. And why would they want to  
13 be on the more conservative side?

14 A. Because they're a regulatory  
15 agency. I don't know.

16 Q. Do you think it might have  
17 anything to do with not wanting people to  
18 get cancer?

19 MS. THOMPSON: Object to  
20 form.

21 THE WITNESS: I'm sure they  
22 don't want people to get cancer.

23 BY MR. VAUGHN:

24 Q. And so setting that lower kg

1 rate gives them a little bit more  
2 assurance, right?

3 MS. THOMPSON: Objection.  
4 Form.

5 THE WITNESS: Not  
6 necessarily, but that's what they  
7 chose to do.

8 BY MR. VAUGHN:

9 Q. What do you mean not  
10 necessarily? Isn't timesing something by  
11 50 going to result in a lower number than  
12 timesing something by 70?

13 MS. THOMPSON: Objection to  
14 form.

15 THE WITNESS: Every time.

16 MR. VAUGHN: All right.

17 Sorry. I got off. I don't know  
18 where I was at.

19 BY MR. VAUGHN:

20 Q. Doctor, you also listed the  
21 FDA's February 2021 "Control of  
22 Nitrosamine Impurities in Human Drugs:  
23 Guidance For Industry" on your list of  
24 your materials considered.

1 Do you recall reading that  
2 document?

3 A. I do.

4 Q. And did you read that entire  
5 document?

6 A. I probably scanned that one  
7 in case there was something different  
8 than what I had seen before. I don't --  
9 I don't remember specifically if I read  
10 the entire word for word.

11 Q. You don't recall if FDA's  
12 guidance document lays out a different  
13 methodology than the one that you used in  
14 forming your opinions?

15 A. Well, I believe the document  
16 that you just have up there now used a  
17 different methodology than I used.

18 Q. And why did you decide to  
19 use a different methodology than the FDA?

20 A. They have a different focus.

21 Q. Is their focus more on  
22 patient health and your focus is more on  
23 defending a pharmaceutical company?

24 MS. THOMPSON: Objection.

1 Form.

2 THE WITNESS: Well, my focus  
3 was on the science behind looking  
4 at a non-cancerous dose as opposed  
5 to trying to extrapolate something  
6 over 70 years in a 50-kilogram  
7 person, which I think is their  
8 more regulatory approach. I tried  
9 to look at the science and  
10 conclude what was available.

11 BY MR. VAUGHN:

12 Q. You didn't even look into  
13 like, mutagenicity and stuff, did you?

14 MS. THOMPSON: Object to  
15 form.

16 THE WITNESS: I'm not sure  
17 what you're asking.

18 BY MR. VAUGHN:

19 Q. That's fine. We'll get into  
20 it more.

21 MR. VAUGHN: Tyler, can you  
22 pull up the 2021 guidance for  
23 industry.

24 And what exhibit number is

1           this going to be, Tyler? I'm  
2           sorry. Is it five?

3                   TRIAL TECH: This is going  
4           to be six.

5                   MR. VAUGHN: Six. Thank  
6           you.

7                   (Document marked for  
8           identification as Exhibit  
9           Bottorff-6.)

10   BY MR. VAUGHN:

11           Q. I'm trying to stay organized  
12   as we go. Can we go to -- this is what I  
13   want to go to 24.

14                   MR. VAUGHN: Can we go to 24  
15   now, Tyler. Sorry about that.

16   BY MR. VAUGHN:

17           Q. All right. If we go --

18                   MR. VAUGHN: Sorry. You  
19   were at the page I wanted.

20                   TRIAL TECH: Okay. I was  
21   going to say, it doesn't look like  
22   there's a Page 24. But this is  
23   the last one.

24                   MR. VAUGHN: The last one.

1           That's what I meant. Of the  
2           document, Page 24 -- or of the  
3           PDF.

4   BY MR. VAUGHN:

5           Q. All right. And, Doctor, if  
6           we go to Line 39. Do you see where the  
7           FDA in this 2021 guidance to the industry  
8           is still recommending that 50 kg be  
9           utilized when doing conversions to  
10          humans?

11                         Doctor?

12                       MR. REEFER: Excuse me,  
13           Brett. Can you hear me?

14                       MR. VAUGHN: I can. Can you  
15           guys not hear me?

16                       MR. REEFER: We're having  
17           some technical difficulties in the  
18           room. I apologize for  
19           interjecting. This is Jason from  
20           the Pietragallo firm.

21                       MR. VAUGHN: No problem.  
22           You guys -- is it fixed now?

23                       MS. THOMPSON: No. We're on  
24           this computer only. So I'm trying

1 to shut down and redo my  
2 connection since I control the  
3 mic.

4 THE VIDEOGRAPHER: Should we  
5 go off the record?

6 MR. VAUGHN: Go off the  
7 record. Yeah.

8 THE VIDEOGRAPHER: The time  
9 right now is 2:52 p.m. We're off  
10 the record.

11 (Short break.)

12 THE VIDEOGRAPHER: The time  
13 right now is 2:57 p.m. We're back  
14 on the record.

15 BY MR. VAUGHN:

16 Q. Doctor, is the amount of  
17 P450-2E1 going to impact how much NDMA it  
18 takes to kill an animal?

19 A. Not necessarily.

20 Q. What do you mean by not  
21 necessarily?

22 A. Well, you can give a massive  
23 IV dose that goes -- that totally  
24 disrupts liver function and causes



1 massive bleeding which has been done and  
2 that has nothing to do with 2E1.

3 Q. Line 39, I don't know if we  
4 got the question in before you guys  
5 disconnected earlier. The FDA here in  
6 2021 is still recommending to use 50 kg  
7 as the body weight, correct?

8 MS. THOMPSON: Objection.  
9 Form.

10 THE WITNESS: I don't think  
11 they are recommending that I or  
12 anyone else use 50 kilograms.  
13 It's what they did in their  
14 calculation.

15 BY MR. VAUGHN:

16 Q. And they're still doing that  
17 calculation in 2021 with 50 kilograms,  
18 correct?

19 A. Correct.

20 Q. And so, on that example we  
21 gave earlier, that one nanogram per  
22 kilogram for human, with your  
23 methodology, you would come out at 70  
24 nanograms. Based on the FDA's

1 methodology, it would be 50-nanograms,  
2 correct?

3 A. Yeah. And we can apply that  
4 to my calculations where the .1 milligram  
5 per kilogram dose that doesn't appear to  
6 cause cancer in rats, we can multiply it  
7 by 50 and I get 5,000 milligrams instead  
8 of 7,000 milligrams. And that wouldn't  
9 change my conclusions at all.

10 Q. Down at the -- towards the  
11 bottom, Line 52. It's talking about TD50  
12 values. Do you know what a TD50 value  
13 is?

14 A. I do.

15 Q. Can you explain to the jury  
16 what a TD50 value?

17 A. It's the dose given to the  
18 animal that you've decided to give it to  
19 that kills half of the animals. It's  
20 sort of like the lethal 50 dose.  
21 Actually it's -- in this case, it's the  
22 tumor dose. It gives half the animals  
23 tumors.

24 Q. The amount that's needed per

1 kg is half as much for a rat as it is for  
2 a mouse, isn't it?

3 A. Yes.

4 Q. And you don't know if that's  
5 because of P450-2E1 or if it's because as  
6 you increase weight it's not proportional  
7 of the dose that you need to give the  
8 animal, correct?

9 MS. THOMPSON: Objection.  
10 Form.

11 THE WITNESS: It's correct  
12 that I don't know what the reason  
13 for that is. It could be that  
14 the -- that the rat are more  
15 resistant to getting tumors than  
16 the mice.

17 I mean, there is a number of  
18 reasons why that might be the  
19 case.

20 BY MR. VAUGHN:

21 Q. You never investigated what  
22 that reason is in forming your opinions,  
23 did you?

24 A. I did not.

1 Q. And if the reason is because  
2 it's not a linear relationship when you  
3 increase weight to dose, then that would  
4 significantly impact your opinions,  
5 wouldn't it?

6 MS. THOMPSON: Objection.  
7 Form.

8 THE WITNESS: No. In fact,  
9 the FDA used the milligram per  
10 kilogram in their calculations. I  
11 mean, so they're comfortable using  
12 milligrams per kilogram.

13 BY MR. VAUGHN:

14 Q. The FDA did in this example.  
15 But what I'm saying is if the rat is  
16 increasing in weight, but only needs half  
17 as much per kilogram, then that's more  
18 like a 50 percent ratio, right, as  
19 opposed to the 100 percent ratio?

20 MS. THOMPSON: Objection to  
21 form.

22 THE WITNESS: This means  
23 that it takes less drug by about  
24 half in the rat versus the mouse

1 to cause a tumor in half of them.

2 BY MR. VAUGHN:

3 Q. And if that held true as the  
4 weight kept going up all the way to a  
5 human and we use the FDA's 50 kg, then  
6 that would only be -- half of 50 is 25,  
7 right? So you'd multiply it by 25  
8 instead, if this held true for humans,  
9 correct?

10 A. Again, we're not applying  
11 the mouse data to the humans.

12 Q. You're not applying the  
13 mouse data to the human?

14 A. And nor did any of the other  
15 studies that I looked at.

16 Q. And you didn't consider the  
17 mouse data?

18 MS. THOMPSON: Objection to  
19 form.

20 THE WITNESS: I did not.  
21 Sorry.

22 BY MR. VAUGHN:

23 Q. I don't know if -- did you  
24 answer that? I don't see it on -- oh,

1     there it is. My internet is now  
2     unstable. Are you able to hear me?

3             A. I think I said correct.

4             Q. You did. I guess my  
5     internet was having -- was going a little  
6     slow there.

7                     So there is a citation for  
8     this, isn't there? Citation Number 3.  
9     And what is that citation?

10            A. In the document?

11            Q. Yeah.

12            A. It's this carcinogenicity  
13     potency database for NDMA.

14            Q. And who published that  
15     database?

16            A. I'm not sure publishes it.  
17     But this is a reference to the National  
18     Library of Medicine collection of those  
19     databases.

20            Q. Is that what the NLM part of  
21     that -- and then it has a ".NIH"; is  
22     that -- what's the NIH part there?

23            A. I guess that's indicating  
24     that the National Library of Medicine is

1 part of the NIH.

2 Q. And that's the National  
3 Institute of Health, correct?

4 A. Correct.

5 Q. And that's what we were  
6 talking about earlier, the National  
7 Institute of Health that continues to  
8 fund Dr. Panigrahy -- sorry. Scratch  
9 that.

10 That's the same National  
11 Institute of Health that we talked about  
12 earlier that continues to fund  
13 Dr. Panigrahy's cancer research, correct?

14 A. Correct.

15 MS. THOMPSON: Object to  
16 form.

17 BY MR. VAUGHN:

18 Q. It's a hard name sometimes.  
19 Doctor, do you know what the  
20 average rate -- I can't talk anymore.

21 Doctor, do you know what the  
22 average weight of a rat was that was  
23 studied with NDMA?

24 A. I looked at that, because in

1 some cases it wasn't so clear what that  
2 number was. And in other cases it was  
3 more clear.

4 Most of these rats were in  
5 the 300, 350, 400, 450 range, depending  
6 on their age and whether they were male  
7 or female.

8 Q. And the mice, did you  
9 calculate their average weight too?

10 A. I did not.

11 Q. You didn't calculate their  
12 weight at .025 kg?

13 A. I did not.

14 MR. VAUGHN: Go to his  
15 expert report. Go to Page 44.

16 BY MR. VAUGHN:

17 Q. On Line 728, where you note  
18 the rough estimate of 25 grams or 0.025  
19 kg for the mice, what did you base that  
20 off of? Or do you not recall putting  
21 that into your expert report?

22 A. No, I recall. This was one  
23 of the mice studies that I looked at, and  
24 I don't believe in the paper they



1 actually reported the weights.

2 So to do my calculation, I  
3 had to go to the laboratory animal place  
4 where you go buy them and look at that  
5 specific strain and then look at the  
6 weights that they give.

7 Q. Did you not look at any  
8 other NDMA studies in mice to see what  
9 weights they were in those studies?

10 A. No. I don't recall any  
11 other one.

12 Q. Why didn't -- why didn't you  
13 do that?

14 A. As I did my search and  
15 started looking for articles that had  
16 some kind of dose-response relationship  
17 that would indicate a non-cancerous dose,  
18 the vast majority of that data were in  
19 rats. And so I used predominately rat  
20 data.

21 Q. Did you give more weight to  
22 the rat data just because more studies  
23 have been done in rats?

24 A. No. As I said earlier, I

1 gave more weight because many of these  
2 researchers talk about how the rat liver  
3 metabolism is the closest to human liver  
4 metabolism, which is why I think there's  
5 way more rat studies in this area than  
6 there is any other species.

7 Q. So you wouldn't exclude any  
8 animal data just because it wasn't a rat,  
9 right?

10 A. It depends on the data are  
11 and what they found and how they got it.

12 Q. So, like, if the data showed  
13 that it increased the risk of cancer for  
14 another animal, you wouldn't discount  
15 that animal just because it wasn't a rat,  
16 right?

17 A. No, I wouldn't discount  
18 that. But again, I was looking for doses  
19 that didn't cause cancer, not doses that  
20 did. And many of these are on the doses  
21 given to cause cancer.

22 Q. But you wouldn't exclude an  
23 animal just because it wasn't a rat?

24 A. I wouldn't exclude looking

1 at the study. But I might exclude  
2 pharmacokinetic data or something else  
3 that is less applicable to what my  
4 question was.

5 Q. What about just not  
6 mentioning it in your study, like the  
7 animal. Like, you only focus on the rat  
8 when the study looked at rats and another  
9 animal?

10 A. I think it was appropriate  
11 to focus on the rat because that's the  
12 animal that best approximates metabolism,  
13 which is what the focus of my report was.

14 Q. Right. You don't even know  
15 what the metabolism is in a mouse. So  
16 how do you know that the rat is the  
17 closest to a human?

18 MS. THOMPSON: Objection.  
19 Form.

20 THE WITNESS: Because of all  
21 the studies that I looked at.

22 BY MR. VAUGHN:

23 Q. What's a hamster? How close  
24 is that to a human?

1 MS. THOMPSON: Objection.

2 Form.

3 THE WITNESS: I don't know  
4 for sure. I know studies have  
5 been done. But not that many.

6 MR. VAUGHN: Can we go to  
7 Page 46 of your expert report now.  
8 And can we go to Line 766.

9 BY MR. VAUGHN:

10 Q. And can you read the  
11 sentence for the jury that starts with  
12 "rats"?

13 A. "Rats and hamsters were  
14 studied, but given the preponderance of  
15 rat studies, only the rat data are shown  
16 here."

17 Q. Is this consistent with what  
18 you just testified to?

19 A. Yes.

20 Q. How?

21 A. That the preponderance of  
22 evidence comes from rat data.

23 Q. And so you discounted the  
24 hamster data because it wasn't a rat,

1 right?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: I did not  
5 include it because the rats are  
6 the closest and I wanted to look  
7 at as many rat studies as I could.

8 BY MR. VAUGHN:

9 Q. And again, how can you say  
10 that rats are closer to humans than  
11 hamsters if you don't know what hamsters'  
12 metabolism is like?

13 A. When the researchers in my  
14 research say rats are closest, I believe  
15 them.

16 Q. So you would defer to  
17 someone else on that, correct?

18 MS. THOMPSON: Objection.

19 Form.

20 THE WITNESS: For the people  
21 who do animal studies in this  
22 area, yes, I would.

23 BY MR. VAUGHN:

24 Q. So, like, a cancer

1 researcher that focuses on animal  
2 studies, you would defer to that cancer  
3 researcher, correct?

4 A. I would refer to the study,  
5 regardless of who the researcher was.

6 Q. Defer?

7 A. I would defer to their  
8 conclusion that they chose that animal  
9 for a reason.

10 Q. And so if a cancer  
11 researcher with a specialty in animal  
12 studies says that some other animal  
13 besides a rat is closest to a human in  
14 how they metabolize NDMA, you would defer  
15 to that cancer researcher, correct?

16 MS. THOMPSON: Objection to  
17 form.

18 THE WITNESS: I would look  
19 at that, yes.

20 BY MR. VAUGHN:

21 Q. Would you defer to them?

22 MS. THOMPSON: Objection.  
23 Form.

24 THE WITNESS: Again, if it's

1           one study, no. If it's, as in  
2           this case, dozens and dozens of  
3           studies that said that about the  
4           rat, then I would defer to the rat  
5           studies.

6 BY MR. VAUGHN:

7           Q. But again, you don't know  
8           about how other animals compare to humans  
9           when it comes to their metabolism of  
10          NDMA, correct?

11          A. Well, that's not true. I  
12          have looked at that.

13          Q. Okay. Hamsters, did you  
14          look at hamsters?

15          A. I read the study. But I  
16          don't recall the hamster data.

17          Q. Okay. But -- sorry?

18          A. That's okay.

19                 As I previously testified, I  
20          did look at the swine data. I did look  
21          at the beagle data. I did look at the  
22          monkey data.

23          Q. But not the hamster or the  
24          mouse?

1           A.       Well, I did report on a  
2 mouse study. I just didn't report on a  
3 hamster study.

4           Q.       But you didn't look into  
5 either a mouse or a hamster as it relates  
6 to metabolism of NDMA, correct?

7           A.       I did one mouse study. We  
8 just looked at it.

9           Q.       But that had to do with how  
10 the mouse metabolizes NDMA?

11          A.       I think it had to do with  
12 alcohol and the effects of NDMA.

13          Q.       And what impact does alcohol  
14 have on NDMA?

15          A.       Go back to the study --  
16 which one was it? Will someone refresh  
17 my memory where it was.

18                   MS. THOMPSON: Page 44.

19                   THE WITNESS: Page --

20                   MS. THOMPSON: 44.

21                   THE WITNESS: 44?

22                   Oh, the Gricute.

23 BY MR. VAUGHN:

24          Q.       Where in that paragraph that



1 you're talking about on Page 44 that you  
2 discuss the metabolism of NDMA in mice?

3 A. I don't. I'd have to pull  
4 the study to see why I only put this  
5 amount of data in. But it was trying to  
6 get at what was the dose that was being  
7 studied.

8 And again, my focus for this  
9 report was to try to find studies that  
10 gave doses that did not produce cancer.

11 And they gave such a large  
12 dose, that it didn't give me evidence  
13 with which to reach my conclusions.

14 Q. So in forming your opinions,  
15 you only considered data or studies that  
16 did not cause cancer, you didn't consider  
17 the ones that did cause cancer, correct?

18 MS. THOMPSON: Objection.

19 Form.

20 THE WITNESS: Untrue,  
21 because many of these studies also  
22 caused cancer. But what I was  
23 interested in is if they had dose  
24 regimens small enough to allow me

1 to evaluate a noncancer-causing  
2 dose and what that dose was and  
3 how it correlated to the amount of  
4 NDMA in the valsartan products.

5 BY MR. VAUGHN:

6 Q. Did you try and look for any  
7 literature on low doses causing cancer in  
8 animals?

9 MS. THOMPSON: Objection.  
10 Form.

11 THE WITNESS: I think, in a  
12 way that's what I just said, is I  
13 looked for studies that had enough  
14 of a low dose of the dosage range  
15 on the low end, to have a low  
16 enough dose to not cause cancer,  
17 if that existed. And if it didn't  
18 exist, it didn't. But it did.

19 BY MR. VAUGHN:

20 Q. Were you only looking for  
21 ones where it did not cause cancer?

22 MS. THOMPSON: Objection.  
23 Form.

24 THE WITNESS: If there were

1 low dose studies that did cause  
2 cancer, I looked at them and I  
3 included them. But I was focusing  
4 on low dose studies that had an  
5 arm that didn't cause cancer so I  
6 could try to find how that low  
7 dose noncancer-causing dose  
8 related to NDMA in valsartan.

9 BY MR. VAUGHN:

10 Q. So any low dose studies that  
11 did cause cancer would be contained in  
12 the body of your expert report, correct?

13 A. Well --

14 Q. Let me rephrase that. So  
15 any low dose studies that did cause  
16 cancer that you relied on in forming your  
17 opinions in this case would be contained  
18 in the body of your expert report,  
19 correct?

20 A. I believe so, yes.

21 Q. I see a 1978 document from  
22 the WHO on nitrosamines on your materials  
23 considered list.

24 What is the WHO?

1           A.     The World Health  
2     Organization.

3           Q.     Is that a reputable  
4     organization?

5           A.     Yes.

6           Q.     Is that an authoritative  
7     organization?

8           A.     Yes.

9                     MR. VAUGHN: Tyler, do you  
10     mind pulling the -- yeah, 2002  
11     WHO.

12                     (Document Marked for  
13     identification as Exhibit  
14     Bottorff-7.)

15     BY MR. VAUGHN:

16           Q.     Did you review anything  
17     after the 1978 one? I don't see this  
18     2002 one on your materials considered.

19           A.     I have one that's dated  
20     2002. So I have looked at this.

21           Q.     Oh, good. Is it included on  
22     your materials considered?

23           A.     I don't know. But I  
24     actually looked at this, I don't know, a

1 couple days ago. So I know I've seen it.

2 Q. Did you consider it when  
3 forming your opinions in this case?

4 A. We're looking for it. I  
5 don't know.

6 Q. All right. 2002 is a lot  
7 more recent than 1978, isn't it?

8 A. Yes.

9 Q. A lot has changed, you know,  
10 from 1978 to 2002 in science. Wouldn't  
11 you agree?

12 MS. THOMPSON: I'm giving  
13 him the list of materials  
14 considered.

15 BY MR. VAUGHN:

16 Q. I could have missed it. So  
17 please double-check and let me know if  
18 you included that on your materials  
19 considered.

20 A. Yeah, I have the article. I  
21 know I looked at it. I just don't see it  
22 at this point on the materials  
23 considered.

24 Q. Do you recall anything in

1 this document that is counter to your  
2 methodology?

3 A. Not that I recall.

4 Q. Would you want your  
5 methodology to be counter to what the WHO  
6 recommends?

7 MS. THOMPSON: Objection.

8 Form.

9 THE WITNESS: It depends on  
10 what they're recommending. So I  
11 don't know -- I don't know how to  
12 answer that.

13 BY MR. VAUGHN:

14 Q. It's fine. I'll be a little  
15 more specific for you.

16 MR. VAUGHN: Tyler, do you  
17 mind taking us to PDF Page 27. I  
18 think it's 23 on the bottom of the  
19 document though.

20 BY MR. VAUGHN:

21 Q. I guess before we do that,  
22 this n-nitroso -- how do you say that?

23 A. N-nitrosodimethylamine.

24 Q. What is that?

1 A. That's NDMA.

2 Q. So this document is specific  
3 to NDMA?

4 A. Yeah. And I did find this  
5 in my -- in my documents that I reviewed.

6 Q. It's on your materials  
7 considered list?

8 A. Very top of Page 5.

9 Q. Okay. See, I do -- oh, but  
10 WHO is further in there. That's why I  
11 missed it. Thank you for pointing that  
12 out.

13 A. No problem. I know I had  
14 seen it.

15 Q. Appreciate it.

16 MR. VAUGHN: So yeah, now,  
17 can we go to Page 27 of the PDF,  
18 Tyler.

19 BY MR. VAUGHN:

20 Q. And then under dose-response  
21 analysis, can you read that entire second  
22 paragraph for the jury, Doctor?

23 A. "Scaling for variations in  
24 the ratios of surface area to body weight

1 between rodent species and humans was not  
2 considered appropriate for the measures  
3 of exposure response developed on the  
4 basis of experimental data in animals,  
5 since it's highly probable that the  
6 carcinogenicity of NDMA is mediated  
7 primarily through the generation of an  
8 active metabolite."

9 Q. What do you understand that  
10 to mean?

11 A. That means that they chose  
12 not to use body surface area, which you  
13 use body weight when you calculate body  
14 surface area. So they're saying they  
15 chose not to use body surface area.

16 Q. So they didn't scale between  
17 species to humans?

18 A. Not using body surface area.

19 Q. How did they recommend  
20 scaling?

21 A. Well, this doesn't say what  
22 they recommended for that.

23 Q. And what's the reason they  
24 are saying not to scale based on surface



1 area to body weight?

2 A. Again, I'm not sure how they  
3 derived their reason. But the reason  
4 they list is mediation through the active  
5 metabolite generation.

6 Q. And what active metabolite  
7 is that?

8 A. The methyldiazonium ion  
9 mediated by 2E1, which we previously  
10 talked about the rat model being a good  
11 approximation of humans for that.

12 Q. Were you aware that you  
13 shouldn't be using surface area to body  
14 weight conversions with NDMA?

15 A. I don't recall specifically  
16 that comment. But in all these studies,  
17 they've used body weight. So that's  
18 almost like saying that it's the accepted  
19 way to do that, instead of body surface  
20 area.

21 Q. Your opinion is it's almost  
22 like saying it's accepted to do it the  
23 way you did?

24 A. I would say that if I did it

1 using body surface area, I would have  
2 been wrong in their opinion.

3 Q. This active metabolite, is  
4 that a genotoxin?

5 A. That is the genotoxin.

6 Q. So is it because it is a  
7 genotoxin they're saying not to do the  
8 scaling?

9 MS. THOMPSON: Objection to  
10 form.

11 THE WITNESS: Not to my  
12 knowledge.

13 BY MR. VAUGHN:

14 Q. It says "since it's  
15 highly probable". Isn't "since" kind of  
16 like "because", this is the reason we're  
17 telling you not to do it?

18 MS. THOMPSON: Object to the  
19 form.

20 THE WITNESS: I think so.  
21 But it's -- I think you could  
22 argue it's metabolism, not the  
23 genotoxicity that makes that  
24 statement.

1 BY MR. VAUGHN:

2 Q. What do you derive that from  
3 in this paragraph?

4 A. Because they don't say we  
5 recommend this because it's a genotoxin.  
6 They recommend it because of the active  
7 metabolite pathway.

8 Q. If it was recommended  
9 because it was a genotoxin, would that  
10 change the way you did your methodology?

11 MS. THOMPSON: Objection.  
12 Form.

13 THE WITNESS: Yeah,  
14 possibly. But that's not what  
15 they are saying.

16 BY MR. VAUGHN:

17 Q. Okay. And you've never  
18 worked with a genotoxin prior to this  
19 litigation, correct?

20 MS. THOMPSON: Objection.  
21 Form sorry.

22 THE WITNESS: Sorry. What  
23 do you mean by work?

24 BY MR. VAUGHN:

1 Q. Did you not testify earlier  
2 that you have not had experience with  
3 genotoxins prior to this litigation?

4 A. I don't think that's exactly  
5 how I worded it because I think you did  
6 use the word "work with," and I wanted  
7 you to define it.

8 Q. And I said, you know,  
9 anything. I tossed some examples and I  
10 said in any way. And you said no. I  
11 mean, can you think of one now?

12 A. No, I said that I had looked  
13 at Actos and its genotoxicity. And that  
14 I've taken care of hundreds of patients  
15 who were cardiac transplant patients that  
16 were on immunosuppressive drugs that have  
17 the potential to be genotoxic. So it's  
18 not a foreign concept to me at all.

19 Q. How much immunosuppression  
20 is necessary to be genotoxic?

21 A. I'm not sure. It's not how  
22 those drugs are dosed. The  
23 immunosuppressive is dosed to prevent the  
24 more problem at hand, which is the organ

1 transplant. So they're not dosed based  
2 on their genotoxic potential. It's an  
3 unwanted side effect if it were to occur.

4 Q. Are you aware if NDMA is an  
5 immunosuppressant?

6 A. I'm not aware of that. I  
7 focused on its metabolism.

8 Q. And so you didn't consider  
9 if NDMA was an immunosuppressant when  
10 forming your opinions?

11 A. No. I did not consider  
12 that.

13 Q. Right. Immunosuppressant  
14 itself can cause cancer, correct?

15 MS. THOMPSON: Object to  
16 form.

17 THE WITNESS: I mean, I  
18 think that's a blanket yes/no  
19 statement, and I think it's  
20 probably a lot more complicated  
21 than that.

22 BY MR. VAUGHN:

23 Q. But you didn't evaluate any  
24 other things that you would need to in

1 forming your opinions, right?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: I didn't  
5 evaluate immunosuppression as part  
6 of my opinions.

7 BY MR. VAUGHN:

8 Q. You didn't even consider  
9 immunosuppression, did you?

10 MS. THOMPSON: Objection to  
11 form. Asked and answered.

12 THE WITNESS: I did not.  
13 Metabolism is what I focused on.

14 MR. VAUGHN: How long have  
15 we been going in this section?

16 Have we been on the record a  
17 little bit.

18 THE VIDEOGRAPHER:  
19 28 minutes.

20 MR. VAUGHN: Oh, yeah, we  
21 had that break earlier.

22 Do you need a break, Doctor,  
23 or are you good.

24 THE WITNESS: I'm good.

1 MR. VAUGHN: Anyone else?

2 MS. THOMPSON: No.

3 MR. VAUGHN: All right.

4 Tyler, if we can go back to his  
5 expert report. And let's look at  
6 Page 57 this time.

7 BY MR. VAUGHN:

8 Q. Doctor, can you read aloud  
9 the first two sentences of this page?

10 A. "Notably, in Dr. Panigrahy's  
11 report on Page 31, he states that only a  
12 single dose of NDMA is required to cause  
13 and initiate cancer in multiple animal  
14 species; however, Dr. Panigrahy did not  
15 cite any literature in support of this  
16 assertion. Based on my experience and my  
17 review of the literature, I do not agree  
18 with Dr. Panigrahy's blanket assertion."

19 Q. Dr. Panigrahy, that's the  
20 cancer researcher that we've been talking  
21 a lot about that the NIH funds, right?

22 A. Right.

23 Q. And you don't agree with him  
24 that a single dose of NDMA is capable of

1 inducing cancer, correct?

2 A. I think what I'm stating  
3 here is I don't agree with that statement  
4 without having a reference to it.

5 Q. And did you review all the  
6 literature at the end of Dr. Panigrahy's  
7 expert report?

8 MS. THOMPSON: Objection.  
9 Form.

10 THE WITNESS: I didn't read  
11 every single article that he  
12 referenced.

13 BY MR. VAUGHN:

14 Q. So you didn't come across  
15 any of the literature that supported his  
16 opinion -- or that would support his  
17 opinion that only one dose of NDMA can  
18 cause cancer?

19 A. No. And I did it -- I  
20 commented on it in the context that  
21 follows those two sentences.

22 And it's that, if the dose  
23 is low enough, which was again, the focus  
24 of my contentions, that a single dose



1 would be almost entirely metabolized by  
2 the liver.

3 So I think it would be  
4 better to put it into the context of what  
5 I was referring to.

6 Q. Just to be clear, you did  
7 not review all the literature that Dr.  
8 Panigrahy did, correct?

9 A. Correct.

10 MR. VAUGHN: Can we go to  
11 Page 26 of his expert report now.  
12 BY MR. VAUGHN:

13 Q. Can you read that last  
14 sentence that goes onto the next page.  
15 It starts with, "A key step."

16 A. This is my report, right?

17 Q. Correct. This is your  
18 report?

19 A. "A key step in this  
20 metabolic activation to a potential  
21 carcinogen is the hydroxylation of  
22 NDMA/NDEA by cytochrome P450 pathways.  
23 2E1 is almost exclusively for NDMA, and  
24 both 2E1 and 2A6 are used for NDEA."

1 Q. And you have a citation  
2 there, don't you?

3 A. Yes.

4 MR. VAUGHN: And can we  
5 scroll down to see what that  
6 citation is.

7 BY MR. VAUGHN:

8 Q. You found these authors of  
9 this article to be credible, correct?

10 A. Correct.

11 Q. And experienced in the field  
12 of nitrosamines?

13 A. I didn't look at each author  
14 or even the first author's complete  
15 publication list to see how many papers  
16 they've written in that area. I've just  
17 focused on what this one said.

18 Q. But the more papers they  
19 wrote on it, probably the more  
20 authoritative they are?

21 A. Potentially, yes.

22 MR. VAUGHN: Tyler, can we  
23 go back now to Exhibit B, his  
24 materials relied on. Let's go to

1 PDF Page 9. It's Page 8 on the  
2 bottom of the document.

3 BY MR. VAUGHN:

4 Q. Doctor, if you look up about  
5 five rows, you'll see this Kushida.  
6 That's the article that you were citing  
7 to a second ago in your expert report,  
8 right?

9 A. Yes.

10 Q. Do you see the -- oh, I  
11 think it's about the sixth, the  
12 next-to-last name, T. -- I don't know  
13 how you say that. Nohmi?

14 A. Mm-hmm. I see it.

15 Q. Do you recall if you  
16 reviewed any other articles by this T.  
17 Nohmi?

18 A. I don't think I did. I  
19 don't recall that.

20 Q. Do you recall seeing other  
21 papers by this T. Nohmi in Dr.  
22 Panigrahy's expert report?

23 A. I may have seen that. But I  
24 didn't read those.

1 Q. Okay. Well, let's have a  
2 look at those.

3 MR. VAUGHN: Tyler, will you  
4 pull up the Nohmi 2020 for us.

5 (Document marked for  
6 identification as Exhibit  
7 Bottorff-8.)

8 BY MR. VAUGHN:

9 Q. This first one that we were  
10 looking at that you cited to is back in  
11 2000. And this one now is in 2020. So  
12 this -- Nohmi has at least been, you  
13 know, involved in researching  
14 nitrosamines for 20 years. Would you  
15 agree with that?

16 A. I don't know what happened  
17 in between. So there's a 20-year time  
18 period between these two papers.

19 Q. He was studying nitrosamines  
20 20 years ago, and he's still studying  
21 nitrosamines though in 2020, right?

22 MS. THOMPSON: Object to  
23 form.

24 THE WITNESS: That, I agree.

1 BY MR. VAUGHN:

2 Q. Right.

3 A. That, I agree. I just don't  
4 know what happened in between.

5 Q. You don't know if he's  
6 published additional papers in between  
7 2000 and 2020, like in 2018, right?

8 A. Right. I did not look at  
9 that.

10 MR. VAUGHN: Okay. Then if  
11 we can go down about two-thirds of  
12 the way under that first paragraph  
13 under introduction. And there's a  
14 sentence starting with "In  
15 General."

16 BY MR. VAUGHN:

17 Q. Doctor, can you read that  
18 sentence aloud for the jury?

19 A. "In general, genotoxic  
20 carcinogens are regulated under the  
21 policy that they have no thresholds or a  
22 safe dose."

23 Q. And then how many citations  
24 are listed after that?

1 A. Three.

2 Q. Do you know what ICH stands  
3 for?

4 A. Yeah. I think it's a cancer  
5 harmonization group or something like  
6 that. International cancer harmonization  
7 or something.

8 Q. And they are saying  
9 genotoxic carcinogens are regulated under  
10 the policy they have no threshold or safe  
11 dose. You weren't aware of that when you  
12 were forming your opinions, were you?

13 MS. THOMPSON: Objection.  
14 Form.

15 THE WITNESS: I was aware  
16 that there are people who think  
17 from a regulatory standpoint that  
18 way.

19 BY MR. VAUGHN:

20 Q. Why would regulators take  
21 that stance?

22 MS. THOMPSON: Objection.  
23 Form.

24 THE WITNESS: I'm not a

1 regulator. I don't know.

2 BY MR. VAUGHN:

3 Q. But you agree that a  
4 genotoxin can alter a person's DNA,  
5 correct?

6 MS. THOMPSON: Objection.  
7 Form.

8 THE WITNESS: I agree that  
9 that's the definition of a  
10 genotoxin.

11 BY MR. VAUGHN:

12 Q. But you don't know if that  
13 has any impact on if there should be a  
14 safe threshold, do you?

15 A. Well, on that fact alone,  
16 no, I don't think that's necessarily I  
17 would agree with that.

18 Q. Go ahead and read the next  
19 sentence for us.

20 A. "This is based on the  
21 assumption that even one molecule of  
22 genotoxic chemicals may induce a mutation  
23 that may cause cancer."

24 Q. And then there's a couple

1 citations there as well, correct?

2 A. Correct.

3 Q. Did you happen to read  
4 through of those citations either?

5 A. I did not. They were not  
6 the focus in my report.

7 Q. I thought the focus of your  
8 report was to see how little or how much  
9 NDMA you can -- a human can -- scratch  
10 that.

11 I thought the purpose of  
12 your opinion was to figure out how much  
13 NDMA a person can consume and not get  
14 cancer, right?

15 MS. THOMPSON: Objection to  
16 form.

17 THE WITNESS: Well, again,  
18 there are words in here about  
19 regulatory policy. I didn't  
20 evaluate regulatory policy.

21 There are words in here  
22 about assumption. I didn't  
23 operate on assumptions.

24 I looked at the data. And



1 found that there were doses that  
2 did not cause cancer.

3 BY MR. VAUGHN:

4 Q. And you're not trying to  
5 give any regulatory opinions in this  
6 litigation, correct?

7 A. Correct.

8 MS. THOMPSON: Objection to  
9 form.

10 THE WITNESS: Sorry.

11 MS. THOMPSON: It's okay.

12 THE WITNESS: Correct.

13 BY MR. VAUGHN:

14 Q. The assumption is that one  
15 molecule of a genotoxic chemical may  
16 induce a mutation that may cause cancer.  
17 This sentence though, what does that  
18 actually have to do with regulatory?

19 MS. THOMPSON: Objection.  
20 Form.

21 Where are you reading that  
22 from?

23 THE WITNESS: The second  
24 sentence.

1 BY MR. VAUGHN:

2 Q. Thank you, Doctor.

3 A. Again, the first sentence is  
4 regulatory policy that I said I was not  
5 going to give any opinions on.

6 The second sentence I said  
7 made an assumption and then gave two  
8 references.

9 And so for example,  
10 Panigrahy's report references this  
11 article. And this article only refers to  
12 an assumption.

13 So what I don't know is if  
14 this assumption is referring to papers  
15 that also said assumption as opposed to  
16 data proving it. So I can't really tell  
17 you if this is just somebody repeating  
18 assumption and assumption and assumption  
19 and keep referring to it without having  
20 any evidence or proof. They may have it.  
21 I just can't tell from this.

22 Q. Because you haven't read  
23 this and you haven't read any of the  
24 citations, have you?

1           A.       No. But now I have read  
2 Panigrahy's reference or citation for  
3 that, and there's no data here to support  
4 that contention.

5           Q.       I thought earlier -- I  
6 thought your expert report you said you  
7 did not have anything to support that  
8 opinion?

9                   MS. THOMPSON: Objection to  
10 form.

11                  THE WITNESS: I said he  
12 didn't cite anything to form that  
13 opinion.

14 BY MR. VAUGHN:

15           Q.       So do you think this is the  
16 only article that he based that opinion  
17 on?

18           A.       I do not know that. I know  
19 that this article has no data with which  
20 to make that conclusion that he made.

21           Q.       But you haven't tried to  
22 seek out any additional data regarding  
23 genotoxic chemicals and their ability to  
24 mutate someone's DNA and cause cancer

1 even with just one molecule, have you?

2 A. I haven't looked for that.

3 Although I have found animal data with  
4 way more than one molecule being given  
5 that did not produce cancer over the  
6 entire lifetime of rats which corresponds  
7 to anywhere between 70 and 90 years of  
8 exposure in humans.

9 Q. And because you didn't look  
10 for any literature on this, you cannot  
11 base any of your opinions on the  
12 literature that says this, right? You  
13 didn't -- scratch that.

14 Because you didn't look for  
15 any literature on genotoxic chemicals,  
16 you also did not consider any of that  
17 literature in forming your opinions in  
18 this case; is that correct?

19 MS. THOMPSON: Objection.  
20 Form.

21 THE WITNESS: These opinions  
22 were not germane to the focus of  
23 my report.

24 BY MR. VAUGHN:

1 Q. And explain to me again what  
2 the focus of your report was?

3 MS. THOMPSON: Objection.  
4 Asked and answered.

5 THE WITNESS: The metabolism  
6 of NDMA and NDEA and in relation  
7 to the amounts that were found in  
8 valsartan, and in relation to  
9 that, was there evidence based on  
10 metabolism that there would be a  
11 risk of cancer that I could  
12 identify based on the animal data.

13 BY MR. VAUGHN:

14 Q. Doctor, can you tell the  
15 jury how many molecules of NDMA are in  
16 one nanogram?

17 MS. THOMPSON: Objection.  
18 Form.

19 THE WITNESS: Let's see.  
20 Can we do micrograms  
21 instead?

22 BY MR. VAUGHN:

23 Q. Sure.

24 A. And the reason I say that is

1 this gets back to what are called molar  
2 calculations, which use the molecular  
3 weight of the compound in question, which  
4 in the case of NDMA is -- the molecular  
5 weight is 74. That's the weight of the  
6 carbons an the oxygen and the nitrogens  
7 and the hydrogens.

8 And they add up to 74. So a  
9 microgram divided by 74 would be whatever  
10 that ratio is in micromolar, and a mole  
11 has Avoadra's number, 6.03 times ten to  
12 the 23rd molecules.

13 So we can do that math if  
14 you want.

15 Q. How about this? What's  
16 larger, a nanogram or a molecule?

17 MS. THOMPSON: Objection.

18 THE WITNESS: A nanogram.

19 BY MR. VAUGHN:

20 Q. So there are multiple  
21 molecules of NDMA in every nanogram of  
22 NDMA?

23 A. Right. And so I'm doubting  
24 that there's any way that you could prove

1     that one molecule could cause cancer  
2     because there's no way to give one  
3     molecule.

4             Q.     You're saying they just  
5     can't prove it, so you discount it?

6             A.     And that's why this is an  
7     assumption that I think is being passed  
8     on from person to person.

9                     And in your nursing career,  
10    you may have heard of something called  
11    chart lore where someone has heart  
12    failure, because someone else in a note  
13    said they had heart failure, and you  
14    can't find any evidence of an ejection  
15    fraction or heart failure meds or  
16    anything to substantiate what we call  
17    chart lore.

18                    You can't give one molecule  
19    of anything. We just don't do that.  
20    There's no way to do it. So this is an  
21    assumption that I think is being passed  
22    on.

23             Q.     An assumption based on the  
24    fact that it's genotoxin and can alter

1 someone's DNA, right?

2 MS. THOMPSON: Objection.

3 THE WITNESS: At some dose.

4 But there's no way to prove it  
5 happened at one molecule.

6 BY MR. VAUGHN:

7 Q. Would you say there's 100  
8 molecules in a nanogram? A thousand?  
9 How much do you think there approximately  
10 would be?

11 A. It's based on the molecular  
12 weight of the substance that you're  
13 talking about.

14 Q. It would be more than 100?

15 A. Yeah, because we're talking  
16 6.02 times ten to the 23rd for a  
17 micromole. So that's a lot of molecules.

18 Q. Can you -- we'll go ahead  
19 and do it in micrograms.

20 Can you give me an estimate  
21 of how many of those molecules would be  
22 in a microgram or a nanogram, either one?

23 A. Yeah. That's my estimate.

24 It's -- it's something like times ten to



1 the 20th or something like that.

2 Q. Per, is that microgram or  
3 nanogram?

4 A. Per microgram.

5 Q. And what's ten to the 20th  
6 for the jury?

7 A. Quadrillion billions or  
8 something. I don't know what the exact  
9 is.

10 Q. So per microgram, there's  
11 you said quadrillion billions?

12 A. Oh, I don't know the exact  
13 number. It's got 20 zeros in front of  
14 the decimal point.

15 Q. 20 zeros. And then you are  
16 aware of NDMA levels in valsartan that  
17 are 40 micrograms. So you're saying  
18 billions and billions and billions of  
19 molecules of a genotoxic substance, you  
20 don't think has the potential to cause  
21 cancer, correct?

22 A. At the doses that we're --

23 MS. THOMPSON: Objection.

24 Form.

1 THE WITNESS: At the doses  
2 that we're talking about that have  
3 been demonstrated in the best  
4 approximator we have, which is the  
5 rat, that there is no cancer that  
6 formed in billions times those  
7 billions.

8 BY MR. VAUGHN:

9 Q. Just one nanogram, would  
10 that be like trillions of molecules of  
11 NDMA?

12 A. I'd have to do the math. I  
13 couldn't assign a number to it unless I  
14 did the math. But we're talking about a  
15 lot.

16 Q. So these researchers have a  
17 focus in carcinogens and NDMA. They  
18 think one molecule of it can induce  
19 cancer. And you, a pharmacist, thinks  
20 that trillions of molecules of NDMA won't  
21 even increase the risk of someone getting  
22 cancer; is that correct?

23 MS. THOMPSON: Object to  
24 form.

1 MS. KAPKE: Object to form.

2 THE WITNESS: What is  
3 correct is that there have been no  
4 data showing cancer in humans. So  
5 we have to start there.

6 And just secondly, we have  
7 millions and billions of molecules  
8 being given to rats that don't  
9 cause cancer.

10 And the NDMA in valsartan is  
11 way less than that.

12 So that is what it is.

13 BY MR. VAUGHN:

14 Q. So the only evidence that's  
15 going to be good enough for you is if we  
16 give humans a bunch of NDMA and see what  
17 happens? That's the only way that you're  
18 going to say that it could be a  
19 carcinogen in humans?

20 MS. THOMPSON: Objection to  
21 form. Asked and answered.

22 THE WITNESS: It's not the  
23 focus of my report.

24 The focus of my report is

1           whether the amount in valsartan  
2           that we know, whether that  
3           achieves some likelihood of  
4           causing cancer based on the best  
5           data we have, which are animal rat  
6           data.

7                       And so I concluded what I  
8           did based on that.

9   BY MR. VAUGHN:

10           Q.     Are you aware of the widely  
11           understood principle that animal studies  
12           may simply be underpowered to pick up the  
13           cancer risk at very low levels?

14                   MS. THOMPSON:   Objection.  
15           Form.

16                   THE WITNESS:   I am aware of  
17           any study can be limited by the  
18           lack of something showing up at  
19           low doses.   And that's what we  
20           have.   That's the data that we  
21           have.

22   BY MR. VAUGHN:

23           Q.     And are you aware that Peto  
24           previously stated that too?

1           A.       That Peto stated that we  
2     have data showing that low doses won't  
3     cause cancer?

4           Q.       No, that Peto says that  
5     animal studies were underpowered;  
6     therefore, they wouldn't be able to  
7     detect low doses increasing the risk of  
8     cancer, which is why they extrapolate all  
9     the way down to a no dose threshold.

10                   Are you aware if Peto said  
11    that?

12                   MS. THOMPSON:   Objection to  
13    form.

14                   THE WITNESS:    I am aware of  
15    Peto's study.   I referenced it.   I  
16    referenced the concerns that he  
17    also expressed about the accuracy  
18    of the no threshold concept.

19   BY MR. VAUGHN:

20           Q.       You said you are aware of  
21    Peto study.

22                   Is it your belief that Peto  
23    has only done one study on NDMA?

24           A.       I never said that.   I was

1 referring to the one that I referred to  
2 where he gave a low enough dose that we  
3 could see there was no association with  
4 cancers.

5 Q. Have you read all of Peto's  
6 studies on NDMA?

7 A. I'd have to look at my  
8 reference list. I think I've read at  
9 least one or two others.

10 This was by far the largest.  
11 So the reason he did a 4,000-rat study  
12 was to address those concerns about not  
13 having enough power to detect cancers at  
14 low doses. So he improved his power by  
15 doing what I thought was the largest rat  
16 study, although it turns out that REMS  
17 was almost the same size.

18 Q. I'm going to ask you one of  
19 the questions again because I don't think  
20 I got a clear answer.

21 One second. You said that  
22 you're aware of the Peto study. And you  
23 referenced it.

24 My question was, were you

1 aware that Peto said that he believed the  
2 animal studies were underpowered and,  
3 therefore, were not able to detect the  
4 increased risk of cancer at low doses of  
5 NDMA?

6 MS. THOMPSON: Objection.  
7 Form.

8 THE WITNESS: And in that  
9 paper, was it in his introduction  
10 or in his conclusions?

11 BY MR. VAUGHN:

12 Q. You don't recall where it  
13 was?

14 MS. THOMPSON: Objection.  
15 Form.

16 THE WITNESS: I don't. We  
17 could look it up. My suspicion is  
18 that it's in his introduction to  
19 explain why he chose to do a study  
20 in 4,000 rats, is to address that  
21 concern.

22 BY MR. VAUGHN:

23 Q. That's your suspicion, but  
24 you don't know, do you?

1           A.       No. We can call it up. We  
2       can look at it. I would actually love to  
3       do that.

4           Q.       We might do that in front of  
5       the jury instead.

6                   MR. VAUGHN: Can we go back  
7       to that Nohmi 2020 article,  
8       please.

9                   Can we zoom out a little  
10      bit.

11     BY MR. VAUGHN:

12           Q.       Can you read out loud,  
13     Doctor, the next sentence starting with  
14     "accordingly."

15           A.       "Accordingly, genotoxic  
16     carcinogens are strictly regulated and  
17     not allowed to be used as food additives,  
18     pesticides, or veterinary drugs."

19           Q.       So genotoxic carcinogens  
20     aren't even allowed in veterinary drugs  
21     or pesticides, but it's your opinion that  
22     it's okay for them to be in human  
23     medications; is that correct?

24                   MS. THOMPSON: Objection.



1 Form. Calls for speculation.

2 THE WITNESS: Again, at  
3 doses low enough that don't appear  
4 to increase the risk for cancer,  
5 which is what I found, that is  
6 reporting the science, not making  
7 a regulatory statement, which is  
8 not what I'm attempting to do.

9 BY MR. VAUGHN:

10 Q. Okay. Pesticides, it's not  
11 like low amounts of NDMA are allowed in  
12 pesticides. No NDMA is allowed to be in  
13 a pesticide, right?

14 MS. THOMPSON: Objection.

15 Form. Scope.

16 THE WITNESS: I mean that's  
17 what it says, yes.

18 BY MR. VAUGHN:

19 Q. And same for drugs that you  
20 give to animals, it's not like you can  
21 give a little bit. You can't give any at  
22 all, right?

23 MS. THOMPSON: Objection.

24 Form. Scope.

1 THE WITNESS: Again --  
2 sorry.

3 This is a regulatory  
4 perspective. That's not the  
5 approach I took.

6 BY MR. VAUGHN:

7 Q. Which one -- which approach  
8 would be safer for the public health,  
9 your approach or this approach?

10 MS. THOMPSON: Objection.  
11 Form. Scope.

12 THE WITNESS: Again, you --  
13 you are making the assumption that  
14 one molecule causes cancer which  
15 is an unsubstantiated claim.

16 So the reality is that we  
17 have to look at what did happen,  
18 not at what could or should or  
19 might happen in the future.

20 But I was looking at the  
21 reality of what did happen. And  
22 did I feel that this put patients  
23 at risk for developing cancer at  
24 the amount in the valsartan

1 products.

2 And based on the best  
3 available data that I have access  
4 to, the answer is no, I don't  
5 think it put people at excess  
6 risk.

7 BY MR. VAUGHN:

8 Q. Again, you don't know all  
9 the levels that were in valsartan,  
10 because you never even asked defense  
11 attorneys to provide it to you, did you?

12 MS. THOMPSON: Objection.  
13 Form. Asked and answered.

14 THE WITNESS: I didn't ask  
15 attorneys for that. I took it  
16 from the FDA's website which was  
17 publicly available to all of us.

18 BY MR. VAUGHN:

19 Q. Okay. I mean, I guess,  
20 would you expect that a manufacturer of a  
21 pharmaceutical product would disclose all  
22 of their testing data to the FDA?

23 MS. THOMPSON: Objection.  
24 Form.

1 THE WITNESS: They may have.  
2 But the FDA didn't make it  
3 available to me.

4 And even if we go back, I  
5 think at the very beginning of  
6 this morning, when you talked  
7 about the 120 parts per billion,  
8 let's call that the highest level.  
9 It doesn't change the opinions in  
10 my report anyway.

11 BY MR. VAUGHN:

12 Q. Did you just say parts per  
13 billion? Did you mean parts per million?

14 A. If I said billion, I meant  
15 million.

16 Sorry. The 120 parts per  
17 million, which I think we calculated as  
18 being just under 40 micrograms, like 38  
19 something.

20 And so we're talking about,  
21 instead of the calculations that I did on  
22 20 micrograms, that 120 parts per  
23 million, let's call it 40 micrograms.  
24 And so instead of the amount in the

1 valsartan products that I calculated  
2 being anywhere from 350 to 22,000 times,  
3 you know, it's still 150 to 11,000 times.  
4 So it doesn't change my opinions at all.

5 Q. The fact that you  
6 underestimated the amount of NDMA in a  
7 pill, the fact that you overestimated the  
8 weight of the average human, the fact  
9 that you did a one-to-one ratio when you  
10 scaled it for kg, all of those things  
11 together you don't think really impact  
12 your opinion?

13 MS. THOMPSON: Objection to  
14 form. Mischaracterizes his  
15 testimony.

16 THE WITNESS: No. And just  
17 making some assumptions that I  
18 don't necessarily have to agree  
19 with.

20 There's not a patient in  
21 this country on valsartan for  
22 hypertension at the usual age that  
23 those people are that weigh  
24 50 kilograms.

1 BY MR. VAUGHN:

2 Q. In the United States, right?

3 A. Is there one somewhere?

4 Yeah, probably.

5 Q. I mean, I guess Americans  
6 are heavier on average than people in  
7 other countries, aren't we?

8 A. Yeah, that's true.

9 Q. So --

10 A. Again, we're not talking  
11 about healthy 17-years-olds. We're  
12 talking about potentially unhealthy 50-,  
13 60-, 70-year olds, who again aren't going  
14 to be taking the drug for 70 years. At  
15 most they could have been taking it for  
16 four years.

17 Q. So if a company is making  
18 valsartan and some of their product they  
19 know has a lot of NDMA in it and some of  
20 their product has just a little bit of  
21 NDMA in it, do you think it would be more  
22 appropriate for them to be sending that  
23 high level of NDMA to Americans because,  
24 you know, Americans weigh more than other

1 people do in other countries on average?

2 MS. THOMPSON: Objection.

3 Form. Foundation. Calls for  
4 speculation.

5 THE WITNESS: I don't think  
6 I ever said that. But I don't  
7 think anyone would be doing that  
8 anyway.

9 BY MR. VAUGHN:

10 Q. Why?

11 A. Why would they? I can't  
12 come up with a reason why they would. So  
13 I don't have a why.

14 Q. It would be very unethical  
15 if they were doing that, wouldn't it?

16 MS. THOMPSON: Objection.  
17 Form. Scope.

18 THE WITNESS: If someone  
19 were to do something unethical, it  
20 would be unethical.

21 BY MR. VAUGHN:

22 Q. I mean, if a company was  
23 intentionally sending the higher level of  
24 NDMA product to the United States instead

1 of other countries, that would be  
2 unethical to do, right?

3 MS. THOMPSON: Objection.

4 Form. Asked and answered. Scope.  
5 I mean, this is so far afield from  
6 his opinions in his report, I  
7 don't know what we're doing here.

8 BY MR. VAUGHN:

9 Q. You going to answer the  
10 question, Doctor?

11 A. Yes, I can answer.

12 I can't understand how that  
13 would ever happen. So I don't have an  
14 opinion on something that would never  
15 happen.

16 Q. I agree with you, it's  
17 completely inconceivable someone would do  
18 something like that.

19 Do you agree that a  
20 responsible pharmaceutical company would  
21 disclose all of their testing data and  
22 all of the levels of NDMA that they were  
23 aware of in valsartan to the FDA?

24 MS. THOMPSON: Objection to



1 form.

2 MS. KAPKE: Object to form.

3 MS. THOMPSON: I'm going to  
4 re-raise the issue that was raised  
5 earlier, that that is a general  
6 liability opinion. That's not  
7 about causation. That's not what  
8 we're here to discuss.

9 MR. VAUGHN: Well, I mean,  
10 the FDA has done some calculations  
11 and stuff based on the data that  
12 they're aware of. And this expert  
13 has relied on what the FDA was  
14 aware of.

15 So I think it is applicable.

16 BY MR. VAUGHN:

17 Q. You would expect a  
18 responsible company to disclose all the  
19 data that they are aware of to the FDA,  
20 right?

21 MS. THOMPSON: Same  
22 objection.

23 THE WITNESS: I'm assuming  
24 they did. So I don't know what

1           happened there. It wasn't  
2           anything that I looked at or  
3           relied upon.

4                   MR. VAUGHN: Great. Let's  
5           take a break.

6                   THE VIDEOGRAPHER: The time  
7           right now is 3:55 p.m. We're off  
8           the record.

9                   (Short break.)

10                  THE VIDEOGRAPHER: The time  
11           right now is 4:06 p.m. We're back  
12           on the record.

13 BY MR. VAUGHN:

14           Q. Doctor, can you hear me? It  
15           says my connection is unstable. I think  
16           it's good now.

17           A. I hear you now.

18                   MS. THOMPSON: We hear you.

19 BY MR. VAUGHN:

20           Q. All right. Doctor, are you  
21           aware -- strike that. Just going to talk  
22           clearly.

23                   Doctor, are you aware of how  
24           the FDA selected the valsartan pills that

1 it tested for NDMA?

2 A. No, I'm not, actually. I  
3 got the table that I included in my  
4 report off of the FDA's published  
5 website.

6 Q. And so you're not aware if  
7 the companies sent the valsartan pills to  
8 the FDA to test, correct?

9 A. I do not know that.

10 Q. And, therefore, you don't  
11 know if those companies cherry-picked the  
12 valsartan pills that they decided to send  
13 to the FDA, correct?

14 A. I do not know that.

15 MR. VAUGHN: Thank you very  
16 much for your time today, Doctor.  
17 I have no further questions,  
18 subject to direct.

19 THE WITNESS: Okay. All  
20 right. Thank you, Mr. Vaughn.

21 MS. THOMPSON: We are going  
22 to have some questions. And I  
23 wasn't expecting you to do that.  
24 So give me a second to pull those

1 up.

2 THE VIDEOGRAPHER: Are we  
3 going off the record?

4 MR. VAUGHN: I'm fine with  
5 staying on.

6 MS. THOMPSON: If you don't  
7 mind, I'd really like to go off  
8 for just two minutes just to make  
9 sure that I have all my questions.

10 MR. VAUGHN: As long as it's  
11 just a couple minutes.

12 MS. THOMPSON: Real brief.

13 THE VIDEOGRAPHER: The time  
14 right now is 4:07 p.m. We're off  
15 the record.

16 (Short break.)

17 THE VIDEOGRAPHER: The time  
18 right now is 4:10 p.m. We're back  
19 on the record.

20 MS. THOMPSON: Just a few  
21 questions. Hopefully this will be  
22 quick.

23 - - -

24 EXAMINATION

1 - - -

2 BY MS. THOMPSON:

3 Q. Dr. Bottorff, as a doctor of  
4 pharmacy are you able to and have you  
5 prescribed drugs to patients?

6 A. In the context of physically  
7 writing the prescription, I have done  
8 that.

9 Usually I've done it in an  
10 environment where a physician at some  
11 point would need to come behind and  
12 co-sign it instead of independent  
13 prescriptive authority, although there  
14 are some pharmacists in some states who  
15 have that ability. So yeah, I've  
16 initiated, with co-signature, thousands  
17 of drug therapies.

18 Q. And has that included  
19 prescribing anti-hypertensives like  
20 valsartan or other ARB drugs?

21 A. Valsartan, many of the other  
22 ARBs, and not just for hypertension, but  
23 also for heart failure.

24 Q. And you didn't study

1 valsartan and the other ARBs for their  
2 metabolism or their pharmacokinetics for  
3 the first time for this case, right?

4 A. No. No. Those are drugs  
5 that on a regular basis, when they come  
6 out, I look at their pharmacokinetics,  
7 their pharmacodynamics, their side effect  
8 profile. Because when you have more than  
9 one drug in the category, then you need  
10 to evaluate in what situation would I use  
11 this one versus that one, what's the  
12 strength of their outcome data, as much  
13 clinical information on those drugs as I  
14 can get.

15 And it's not just in my own  
16 interest. I get asked questions about  
17 those issues with these drugs from  
18 physicians, from patients and from  
19 students when I teach.

20 Q. We had some questions  
21 earlier, and I just want to give you an  
22 opportunity to explain it cleanly in a  
23 way that a layperson -- and I am a  
24 layperson -- can understand.

1                   What is first-pass  
2   metabolism?

3                   A.       Every drug that we give  
4   orally that is absorbed towards the  
5   liver, across the small intestine,  
6   undergoes what we would call first-pass  
7   metabolism.

8                   And for some drugs that  
9   clearance is pretty low, for some drugs  
10   it's intermediate, and for some drugs  
11   that clearance rate is really high.

12                  And so the amount of drug  
13   that gets through the liver, then into  
14   the hepatic vein, which then enters the  
15   circulation through the heart, the lungs,  
16   back to the liver, to other organs, is  
17   only occurring if drugs are given at a  
18   dose that exceeds whatever that  
19   first-pass metabolism capability is for  
20   that particular drug.

21                  Q.       So did you have to determine  
22   a first-pass metabolism capability for  
23   valsartan and NDMA?

24                  MR. VAUGHN:   Object to form.

1 THE WITNESS: Sorry. For --  
2 for valsartan, that's what's  
3 reported in the package label and  
4 plenty of studies showing --  
5 that's when we talked about its  
6 bioavailability being between,  
7 what was it, 10 and 35 percent.

8 That's the percent of the  
9 drug that gets through the liver  
10 and does its systemic effects,  
11 because that's a drug that you  
12 want to work on the heart, in the  
13 kidney, on the blood vessels.

14 Can you repeat the question  
15 real quick?

16 BY MS. THOMPSON:

17 Q. I was asking about, did you  
18 have to determine the first-pass  
19 metabolism of both valsartan and then  
20 NDMA --

21 A. Yeah, it's easier for  
22 valsartan because it's supposed to get  
23 through the liver and do its  
24 pharmacologic effect so you can measure



1 the bloodstream to assess  
2 bioavailability.

3 For NDMA, that assessment is  
4 not as exact a science, except for a  
5 couple small rat studies that looked at  
6 it, because you don't want it to get into  
7 the systemic circulation.

8 So -- and the dose is low  
9 enough that you get first complete  
10 first-pass metabolism, you couldn't  
11 measure it in the bloodstream.

12 Q. And before valsartan that  
13 contains NDMA or NDEA gets to the liver,  
14 does it get metabolized anywhere else or  
15 exposed to any organs prior to the liver?

16 A. No. And some drugs do.  
17 There is a fairly robust round of  
18 cytochrome P450 in the small intestine.  
19 So many drugs are first metabolized  
20 there, and then into the mesenteric blood  
21 system directly into the liver.

22 But in looking at this  
23 issue, particularly at 2E1, there is no  
24 2E1 in the small intestine. So there is

1 no pre-systemic metabolism before it gets  
2 to the liver. So all of it occurs in the  
3 liver.

4 Q. And so, how do we know that  
5 the only metabolism that would occur  
6 would be in the liver and not prior to  
7 that?

8 MR. VAUGHN: Object to form.

9 THE WITNESS: Because there  
10 is no metabolism ability present  
11 until you get to the liver.

12 BY MS. THOMPSON:

13 Q. Does first-pass metabolism  
14 apply to both NDMA and NDEA?

15 A. Yes, it does.

16 Q. And you also used a term  
17 earlier today that I'm going to again  
18 make you explain to me like a layperson.

19 Liver saturation, can you  
20 please explain that?

21 A. Again, this sort of gets at  
22 the issue of first-pass metabolism and at  
23 what point do you reach the ability of  
24 the liver to completely clear the dose of

1 that drug.

2 And saturation is a good  
3 term. Some people liken it to, like, how  
4 much water can a sponge hold. And when  
5 you've reached the point where the sponge  
6 can hold no more water, the water gets  
7 past the sponge to wherever it would go  
8 after that.

9 So that's a way of thinking  
10 of a saturation point. It's your ability  
11 to measure it beyond the liver.

12 Q. Were you able to determine a  
13 liver saturation level for NDMA or NDEA?

14 A. Not in the context of what  
15 the actual dose would be based on blood  
16 levels past the liver because it has such  
17 a short half-life it's really difficult  
18 to do.

19 So the surrogate for  
20 measuring post-liver blood level  
21 penetration, if you will, was whether  
22 there was any either adducts or cancers  
23 that occurred past that. So that's where  
24 I came up with that

1 .1-milligram-per-kilogram sort of dose  
2 that, if it does get through the liver,  
3 it doesn't appear to cause any downstream  
4 cancer. So it must be in small enough  
5 amounts that it can't do that.

6 Q. Does NDMA or NDEA accumulate  
7 in the liver if it is ingested every day?

8 A. That's a good question. In  
9 a pharmacokinetic sense, drug metabolism  
10 sense, for a drug to accumulate --  
11 remembering that the liver's job is to  
12 metabolize. And if you can't measure any  
13 downstream, it's because the drug has  
14 been completely metabolized in the liver,  
15 so no drug level accumulation would occur  
16 as long as you weren't exceeding that  
17 capacity on a daily basis.

18 So in the doses that we are  
19 talking about, there would be no drug  
20 level accumulation.

21 Q. If valsartan makes it  
22 through the liver and circulates into the  
23 bloodstream and provides therapeutic  
24 effect, how can you say that NDMA or NDEA

1 in it doesn't make it to that point?

2 A. We touched briefly on this.

3 I don't know how well I explained it.

4 But when a tablet of valsartan is

5 dissolved in the stomach and the upper

6 small intestine and then is absorbed, the

7 way I like to explain it, is that they

8 then go their merry way.

9 They are no longer

10 chemically connected. They have their

11 own separate and independent routes of

12 metabolism and elimination. And so

13 valsartan does what it does, and NDMA and

14 NDEA does what it does.

15 Q. And --

16 A. And those mechanisms do not

17 overlap at all.

18 Q. Is evaluating whether,

19 where, and how a drug is metabolized part

20 and parcel of pharmacokinetics?

21 A. Absolutely. I give examples

22 in my report of drugs whose doses are

23 dramatically different, or in some cases

24 aren't even given at all because

1 first-pass metabolism is so efficient  
2 that the drug would be ineffective.

3 And a real classic example  
4 of that is lidocaine. We don't use it  
5 that much anymore for arrhythmias. But  
6 when it was attempted to be given orally,  
7 first-pass metabolism was so extensive  
8 you've got no clinical effect from  
9 lidocaine. Only if you gave it  
10 intravenously.

11 So measurable kinetics,  
12 clearance, half-life, first-pass  
13 metabolism, that's all dependent on the  
14 route of administration.

15 Q. And in your -- I hesitate to  
16 put a number on there -- almost 40-year  
17 career, have you done this type of  
18 evaluation of whether, how, and where  
19 drugs are metabolized in the body in your  
20 ordinary course of your professional  
21 experience?

22 MR. VAUGHN: Object to form.

23 THE WITNESS: I'm sorry.

24 Hundreds of times. There were how

1           many drugs in the cardiovascular  
2           arena on the market when I  
3           graduated compared to how many are  
4           in the arena now in that 40 years,  
5           how many more.

6                     It's like hundreds and  
7           hundreds more, and I do that for  
8           every one of these drugs.

9   BY MS. THOMPSON:

10           Q.     So the analysis that you've  
11           done here to formulate your opinions, is  
12           it consistent with what you've done in  
13           your professional practice?

14           A.     It is a process for any drug  
15           that I go through. What's its dose, how  
16           effective, what are its side effects,  
17           what's its toxicity, what are the data,  
18           what are the type of data. In many cases  
19           I look at the animal studies in addition  
20           to the human studies when they are  
21           conducted.

22           Q.     And you were asked earlier  
23           about your kind of ultimate opinion that  
24           the presence of NDMA in valsartan, based

1 on all of these factors, does not  
2 increase the risk of cancer in downstream  
3 organs. Do you recall that?

4 A. Yes.

5 Q. Okay. How do you know that?

6 MR. VAUGHN: Object to form.

7 THE WITNESS: It's my best  
8 clinical judgment based on an  
9 evaluation of the trials that have  
10 a dose that did not cause cancer  
11 in the most close animal model for  
12 NDMA metabolism, which is the rat.  
13 I identified a dose that below  
14 which would not cause tumors.

15 And then in the multiple  
16 tables that I provided, I compared  
17 that to the milligram-per-kilogram  
18 dose in the valsartan products  
19 versus extrapolating to humans.  
20 And it was hundreds and hundreds,  
21 and even thousands and in some  
22 cases tens of thousands of times  
23 more.

24 So if we add that evidence,



1           which is the best we'll have,  
2           we're not going to have any  
3           better.

4                     If that's the evidence that  
5           we have of a dose and it doesn't  
6           cause cancer --

7                     (Brief interruption.)

8   BY MS. THOMPSON:

9           Q.       Sorry, Doctor.   If you want  
10   to kind of go back and --

11          A.       Poor child.

12                    So again, using the animal  
13   data, which is the best we have to  
14   extrapolate into humans, a noncancerous  
15   dose of NDMA which was about  
16   .1 milligrams per kilogram -- and that  
17   was fairly consistent across three or  
18   four studies, at least that I looked at.  
19   And you expressed that in a human dose  
20   based on body weight, which is the best  
21   way that we have to do it.

22                    Then you get  
23   valsartan-containing products, even if  
24   you accept the 120 parts per million that

1 we talked about, there are still hundreds  
2 to tens of thousands times more than what  
3 doesn't cause cancer in a rat.

4 Q. I have one more question, at  
5 least for now. We'll see if we have  
6 anything further based on what you just  
7 said. I hate to end on this note.

8 In preparing for this, did  
9 you find a citation in your report that  
10 you need to correct?

11 A. Thank you for bringing that  
12 up.

13 When I went through some of  
14 the epidemiology studies and constructed  
15 my tables showing what I thought -- well,  
16 what is the inconsistency in the data on  
17 the association between NDMA proposed in  
18 dietary and/or environmental exposures,  
19 there were two studies by an author named  
20 Straif.

21 And in my tables I reference  
22 Straif and his data. But the citation I  
23 quote is his other study and not the one  
24 that actually has the data that I have in

1     there. So I just need to switch the  
2     citation to the article that has those  
3     data.

4                     The data are accurate,  
5     they're what I wanted to have in the  
6     report, but his reference is the other  
7     one that I read of his, not the one that  
8     has these data.

9                     MS. THOMPSON: And we'll  
10     provide an updated version with  
11     the correct citation for the other  
12     Straif article. I don't know if  
13     anybody else has anything else  
14     that they wanted to cover.

15                    MR. VAUGHN: I'll be quick  
16     then.

17                             -   -   -

18                             EXAMINATION

19                             -   -   -

20     BY MR. VAUGHN:

21                    Q.     Doctor, when did you realize  
22     that your report had citation errors?

23                    A.     Yesterday afternoon. It has  
24     a citation error.

1 Q. And how did that come to  
2 your attention?

3 A. In just going through the  
4 report and looking at some of where the  
5 data came from. I think it actually it  
6 was one of counsel that picked it up.

7 Q. Did you meet with counsel  
8 prior to this deposition?

9 A. Yes.

10 Q. For how many hours?

11 A. Maybe six hours yesterday.

12 Q. Was yesterday the only day?

13 A. It's the only day that we  
14 met in person.

15 Q. How many days did you meet  
16 not in person or did you -- sorry not  
17 meet. Strike that.

18 Did you also consult or prep  
19 with attorneys by remote meetings?

20 A. There was a remote meeting  
21 on Monday that just lasted a couple  
22 hours.

23 Q. Are those the only two  
24 meetings that you had in preparation for

1 your deposition?

2 A. Yes.

3 Q. I believe, just a few  
4 minutes ago, you testified that NDMA is  
5 not exposed to any organs prior to the  
6 liver. Is that what you meant to say?

7 A. That is not what I said.

8 Q. Okay. So if the transcript  
9 says that -- sorry.

10 A. Yeah, let me clarify.

11 It's not exposed to an organ  
12 with metabolic capability prior to  
13 getting to the liver.

14 Q. In your opinion, correct?

15 A. Yes, in my opinion.

16 Q. But there are several organs  
17 that it touches prior to getting to the  
18 liver?

19 A. Not in a metabolizing  
20 capacity.

21 Q. But you would agree that it  
22 at least touches several organs prior to  
23 getting to the liver, correct?

24 A. It passes through the

1 esophagus in a solid pill form, which is  
2 not where absorption would occur.

3 And then its dissolution to  
4 be able to be absorbed occurs in the  
5 stomach where there is no 2E1. And then  
6 it's absorbed across the small intestine,  
7 which also does not have 2E1. So the  
8 first time it's in a form that can be  
9 metabolized by 2E1 is when it gets to the  
10 liver.

11 Q. When a substance is absorbed  
12 through the small intestine, does  
13 100 percent of it go to the liver or does  
14 some of that blood bypass the liver?

15 MS. THOMPSON: Objection to  
16 form.

17 THE WITNESS: Yeah, the  
18 mesenteric system drains it all  
19 into the liver. It's the  
20 evolution of that defense  
21 mechanism. That's what it's there  
22 for.

23 BY MR. VAUGHN:

24 Q. The evolution, what do you

1 mean evolution of that defense mechanism?

2 A. Our evolution of the liver  
3 doing what it does and the cytochrome  
4 P450 system and other metabolizing  
5 pathways that are not, you know, at hand  
6 here, those evolved as a way of  
7 detoxifying things that we ingested.

8 So the evolution of our  
9 alimentary system and our drug  
10 metabolizing system is the way it is to  
11 be a detoxifying system.

12 Q. So is it your opinion that  
13 because humans have been exposed to  
14 environmental nitrosamines throughout  
15 history, that humans have evolved to be  
16 able to not get cancer from NDMA?

17 MS. THOMPSON: Objection.

18 Form.

19 THE WITNESS: Yeah, it's a  
20 good line of thinking, but many of  
21 these P450s evolved in response to  
22 exposures that may have been other  
23 toxins of other types that had  
24 nothing to do with NDMA.

1 But because they're there  
2 and now we are exposed to NDMA, we  
3 have the capacity to metabolize.

4 BY MR. VAUGHN:

5 Q. So --

6 A. Some of these enzymes are  
7 not so super specific that they evolve  
8 only to handle one potential toxin.

9 Q. And is P450 one of those  
10 that handles numerous toxins?

11 A. Yeah. There are like 250,  
12 300 individually specific cytochrome P450  
13 isozymes.

14 Q. Why haven't humans evolved  
15 to just not be able to get cancer at all?

16 MS. THOMPSON: Objection.  
17 Scope.

18 THE WITNESS: That is beyond  
19 my ability to understand and  
20 answer.

21 BY MR. VAUGHN:

22 Q. But you're able to give an  
23 opinion that we've evolved to be able to  
24 handle NDMA?



1 MS. THOMPSON: Objection.  
2 Form. Mischaracterizes.

3 THE WITNESS: We have  
4 evolved with the ability to  
5 detoxify orally ingested  
6 substances.

7 And I should add, it's a  
8 little more complicated than I'm  
9 portraying.

10 Many of the cytochrome P450s  
11 are involved in endogenous  
12 steroid, hormone, and cholesterol  
13 metabolism. So some of them have  
14 multiple jobs.

15 BY MR. VAUGHN:

16 Q. Do you have an opinion on  
17 what animal a human evolved from?

18 MS. THOMPSON: Object to  
19 form.

20 THE WITNESS: The -- I mean,  
21 I'm pretty sure we evolved from  
22 primates, from nonhuman primates.

23 BY MR. VAUGHN:

24 Q. But you think we metabolize

1 NDMA more like a rat than a nonhuman  
2 primate?

3 MS. THOMPSON: Objection.  
4 Asked and answered.

5 THE WITNESS: I think that  
6 because that's what scientists  
7 have said.

8 BY MR. VAUGHN:

9 Q. Does that really make sense,  
10 if we evolved from a nonhuman primate,  
11 that we're going to metabolize it more  
12 like a rat?

13 MS. THOMPSON: Objection.  
14 Asked and answered.

15 THE WITNESS: You know, why,  
16 I don't know that I have an answer  
17 for. It is just what it is. And  
18 so I observed it, reported on it.

19 BY MR. VAUGHN:

20 Q. You noted lidocaine earlier.  
21 Is Lidocaine a genotoxic carcinogen?

22 MS. THOMPSON: Objection.  
23 Form.

24 THE WITNESS: I don't think

1           so. It's just an example of a  
2           drug that has a very high  
3           first-pass metabolism, and so  
4           giving it orally will never  
5           produce any post-liver effect. So  
6           it's a good example in that  
7           regard.

8       BY MR. VAUGHN:

9           Q.       But the only genotoxic  
10          carcinogen that you have experience with  
11          is Actos, correct?

12                 MS. THOMPSON: Objection.  
13          Form. Mischaracterizes testimony.

14                 THE WITNESS: No. I also  
15          mentioned the immunosuppressive  
16          drugs for heart transplant  
17          patients. But that's pretty much  
18          the extent.

19       BY MR. VAUGHN:

20           Q.       Those are genotoxins?

21                 MS. THOMPSON: Objection.  
22          Form.

23                 THE WITNESS: I'm not sure  
24          their mechanism of cancer

1 production is genotoxic. But they  
2 are carcinogenic.

3 BY MR. VAUGHN:

4 Q. Okay. So the only genotoxic  
5 carcinogen that you have experience with  
6 is Actos?

7 MS. THOMPSON: Objection.  
8 Form.

9 THE WITNESS: In -- in that  
10 specific genotoxic sense, yes.

11 BY MR. VAUGHN:

12 Q. Doctor, is every carcinogen  
13 also a genotoxin?

14 MS. THOMPSON: Objection.  
15 Form.

16 THE WITNESS: I don't think  
17 so. But -- yeah, I don't think  
18 so.

19 BY MR. VAUGHN:

20 Q. Were you an expert in the  
21 Actos litigation at all?

22 A. No. That was just out of my  
23 interest in -- when that report came out  
24 about the potential association with

1 bladder cancer in the normal part of what  
2 I do, is I look at the data and where it  
3 came from, and how solid it is, and what  
4 type of data. And Actos was one of those  
5 drugs that a lot of my heart patients  
6 were on.

7 Q. And so you wanted to  
8 investigate it because you cared about,  
9 you know, if your patients got cancer or  
10 not, right?

11 MS. THOMPSON: Objection.  
12 Form.

13 THE WITNESS: I investigated  
14 it to evaluate the quality of the  
15 data to make a determination in  
16 that regard.

17 BY MR. VAUGHN:

18 Q. And in your opinion does  
19 Actos actually incite bladder cancer or  
20 increase the risk of bladder cancer?

21 MS. THOMPSON: Objection.  
22 Form. Scope.

23 THE WITNESS: Certainly not  
24 anything that I put into my

1 report. But my understanding is  
2 that there was some inconsistency  
3 in that data, so I don't think it  
4 was very clear.

5 BY MR. VAUGHN:

6 Q. Did you keep all of your  
7 patients on Actos?

8 MS. THOMPSON: Objection.  
9 Form.

10 THE WITNESS: To the best of  
11 my knowledge, yes.

12 BY MR. VAUGHN:

13 Q. Do you know if any of them  
14 got bladder cancer?

15 MS. THOMPSON: Objection.  
16 Form. Scope.

17 THE WITNESS: To the best of  
18 my knowledge, no.

19 BY MR. VAUGHN:

20 Q. Are you aware of studies  
21 that have shown that gastric and  
22 colorectal tissues are more efficient at  
23 metabolizing NDMA in humans than in  
24 animals?

1 MS. THOMPSON: Objection.

2 Form.

3 THE WITNESS: I have not  
4 seen that data. It didn't come up  
5 in my research.

6 BY MR. VAUGHN:

7 Q. Is it easier to measure the  
8 bioavailability of valsartan in  
9 comparison to NDMA?

10 A. It's easier in the concept  
11 that we can do that in humans and that  
12 we've not done that with NDMA in humans.

13 Q. Didn't you say earlier it's  
14 not well studied in humans?

15 MS. THOMPSON: Objection.

16 BY MR. VAUGHN:

17 Q. Or it's not studied at all,  
18 I guess, is what you're saying?

19 A. Yeah, there are no  
20 pharmacokinetic studies on NDMA in  
21 humans. Maybe the one that was in  
22 ranitidine that we mentioned earlier  
23 today.

24 Q. So would you agree you don't

1 know actually how much NDMA gets into the  
2 bloodstream?

3 MS. THOMPSON: Objection.  
4 Form.

5 THE WITNESS: Because we  
6 don't measure -- number one, we  
7 don't know in humans. And because  
8 we don't measure it in the animal  
9 studies, I use the surrogates,  
10 whether that was a development of  
11 tumor or adducts.

12 BY MR. VAUGHN:

13 Q. But you agree that you do  
14 not know how much would make it into the  
15 bloodstream in a human, correct?

16 MS. THOMPSON: Objection.  
17 Form. Asked and answered.

18 THE WITNESS: It depends on  
19 the dose.

20 BY MR. VAUGHN:

21 Q. At the doses that we are  
22 discussing -- that your expert report  
23 covers, do you know how much NDMA gets  
24 into the bloodstream of a human?



1 MS. THOMPSON: Objection.

2 Form. Asked and answered.

3 THE WITNESS: In a  
4 quantitative amount in the rat  
5 studies, no.

6 But not enough at the  
7 .1-milligram-per-kilogram dose or  
8 below to induce downstream cancer.

9 BY MR. VAUGHN:

10 Q. My question is more simple  
11 than that. Just strictly in humans, you  
12 do not know how much NDMA would get into  
13 their bloodstream after they consumed  
14 valsartan contaminated with NDMA,  
15 correct?

16 MS. THOMPSON: Objection.

17 Form. Asked and answered.

18 THE WITNESS: We do not have  
19 those data in humans. And so  
20 we're relying on the best  
21 surrogate we have, which is the  
22 animal models, particularly the  
23 rat.

24 BY MR. VAUGHN:

1 Q. And so you would agree that  
2 you do not know how much NDMA would get  
3 into the human bloodstream, correct?

4 MS. THOMPSON: Objection.  
5 Form. Asked and answered.

6 THE WITNESS: Correct. We  
7 do not have those human data.

8 BY MR. VAUGHN:

9 Q. And because you don't have  
10 the data, you can't know, correct?

11 MS. THOMPSON: Objection.  
12 Form. Asked and answered.

13 THE WITNESS: I do not know.

14 MR. VAUGHN: I have no  
15 further questions.

16 MS. THOMPSON: One second.  
17 I think we're done. Sorry.

18 MR. VAUGHN: Not a problem,  
19 Sara.

20 MS. THOMPSON: Okay. Can we  
21 go off.

22 MR. VAUGHN: Yeah.

23 THE VIDEOGRAPHER: The time  
24 right now is 4:38 p.m. We're off

1 the record.

2 \* \* \* \* \*

3 (Excused.

4 (Deposition concluded at  
5 approximately 4:38 p.m. eastern  
6 time.)

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1  
2 CERTIFICATE  
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4

5 I HEREBY CERTIFY that the  
6 witness was duly sworn by me and that the  
7 deposition is a true record of the  
8 testimony given by the witness.

9 It was requested before  
10 completion of the deposition that the  
11 witness, MICHAEL B. BOTTORFF, Pharm.D.,  
12 have the opportunity to read and sign the  
13 deposition transcript.

14  
15 \_\_\_\_\_

16 MICHELLE L. GRAY,

17 A Registered Professional  
18 Reporter, Certified Shorthand  
19 Reporter, Certified Realtime  
20 Reporter and Notary Public

21 Dated: September 20, 2021  
22  
23  
24

(The foregoing certification  
of this transcript does not apply to any  
reproduction of the same by any means,  
unless under the direct control and/or  
supervision of the certifying reporter.)

1 INSTRUCTIONS TO WITNESS

2  
3 Please read your deposition  
4 over carefully and make any necessary  
5 corrections. You should state the reason  
6 in the appropriate space on the errata  
7 sheet for any corrections that are made.

8 After doing so, please sign  
9 the errata sheet and date it.

10 You are signing same subject  
11 to the changes you have noted on the  
12 errata sheet, which will be attached to  
13 your deposition.

14 It is imperative that you  
15 return the original errata sheet to the  
16 deposing attorney within thirty (30) days  
17 of receipt of the deposition transcript  
18 by you. If you fail to do so, the  
19 deposition transcript may be deemed to be  
20 accurate and may be used in court.

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1  
2 ACKNOWLEDGMENT OF DEPONENT  
3

4 I, \_\_\_\_\_, do  
5 hereby certify that I have read the  
6 foregoing pages, 1 - 391, and that the  
7 same is a correct transcription of the  
8 answers given by me to the questions  
9 therein propounded, except for the  
10 corrections or changes in form or  
11 substance, if any, noted in the attached  
12 Errata Sheet.  
13  
14

15 \_\_\_\_\_  
16 MICHAEL B. BOTTORFF, Pharm.D. DATE  
17  
18

19 Subscribed and sworn  
20 to before me this  
21 \_\_\_\_\_ day of \_\_\_\_\_, 20\_\_\_\_.  
22 My commission expires: \_\_\_\_\_  
23

24 \_\_\_\_\_  
Notary Public

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